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THE STORY OF PRENATAL CARE*

PRESIDENTIAL ADDRESS

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BY PRECEDENT, the address of your presiding officer has been directed not to the presentation of some new scientific achievement but rather to the analysis of underlying movements or philosophies that influence our special field of medicine. Sampson spoke to you of "Hobbies," Gellhorn on "Constitutional Factors," Graves on "The Control of Life"; and gracefully worded historical reviews have been presented by Chipman, Keene, Anspach and Watson. Having in mind this year's symposium on the prevention of eclampsia, it seemed fitting and perhaps of some interest to narrate briefly the story of prenatal care.

THE STORY OF PRENATAL CARE

From the beginnings of time the pregnant woman has always been regarded with reverence. Special privileges were granted her and so sacred was her abode that even a murderer seeking shelter under her roof could not be taken forth and killed. If she was physically injured by some one, the punishment was death. If she herself had done some crime, verdict was postponed until her child was born.

Many ancient records contain instructions for the care of pregnant women. A Chinese work enjoins them to avoid rich food, excessive

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exercise and "strange and wonderful preparations." Both the Old Testament and the Talmud give detailed advice concerning the conduct of women in pregnancy. In India the Hindu priests held conclaves in which obstetric nurses were consecrated and instructed in the prenatal and postnatal care of their patients.

Hippocrates and his school centered attention largely on the prevention of abortion. They warned against excessive purgation and coitus. Fear and great excitement might also interfere with the proper development of the pregnancy.

More explicit than Hippocrates was Susruta, writing in India in the second century before Christ. He set forth rules as to food and drink, exercise and clothing. The pregnant woman should be surrounded by cheerful company both for her own and her child's sake. He cautions against marriage with a woman whose family is tainted with epilepsy or tuberculosis.

In the days of the Emperor Trajan lived Soranus of Ephesus who devoted many chapters of his book on gynecology to prenatal care. Concerning the tendency to abortion from physical exertion and trauma, he writes quaintly: "Houses built on a firm foundation stand unshaken a long time, whereas the house that has a bad and loose construction falls under the slightest strain." Wrinkling of the abdominal skin can be avoided by anointing with a wax ointment mixed with oil made of unripe olives and myrtle. Toward the end of pregnancy a warm sitz-bath softens the tissues and produces an easy labor.

In the succeeding centuries and through the middle ages attention was directed largely to the management of labor and no important contributions were made to the study of prenatal care.

In 1584 a French physician, Scevole de Saint-Marthe, wrote a Latin poem entitled "Paedotrophia" (the nurture of children), containing much good advice on prenatal care. It opens with the lines:

> "Don't till 'tis born defer thy Pious care
> Begin betime and for its birth prepare."

Further on it reads:

> "Refresh thy weary limbs with sweet repose
> And when fatigued thy heavy eyelids close.
> Be careful how your meats you choose
> And chosen well, with moderation use."

Not until we come to the great Mauriceau in 1668 do we again find a significant contribution to the hygiene of pregnancy. In his *Maladies des Femmes Grosses* he devotes an entire chapter to this subject, beginning: "The pregnant woman is like a ship upon a stormy sea full of white-caps, and the good pilot who is in charge must guide her with prudence if he is to avoid a shipwreck."

"Fresh air, avoidance of extreme heat or cold, and freedom from smoke and foul odors are essential to her health. She should eat well-cooked

wholesome food in small amounts at intervals rather than at one large meal. Forbidden are highly spiced pastries, for they create gas. Fresh fish caught in streams are better than lake fish. And with this food a bit of good old wine, tempered with water, rather red wine than white wine, aids the digestion. Beware of cold drinks, for did not the Empress of Austria in July, 1677, take strawberries and ice, and abort at the fourth month of her pregnancy?" Since the prominence of the abdomen in pregnancy prevents women from seeing their feet, Mauriceau advises low-heeled shoes which will prevent them from tripping. Stooping in the later months may lead to faulty position of the child and interfere with the somersault that normally brings the head into the pelvis. For constipation he recommends eating apples, stewed prunes, and fresh figs. If necessary, he prescribes a mild enema of marshmallow, pellitory and anise with two ounces of beet sugar and a little oil.

Above all Mauriceau harangues against those terrible whalebone corsets worn by women of the upper classes who wish to conceal to the last moment the fact of their pregnancy. Squeezed from above, the abdomen is distended below. "When the mother finds her abdominal walls wrinkled and pendulous like a bag," he writes, "the poor midwife is accused of not having used the proper ointment, when the real cause lay in the prolonged wearing of the corset." The age-old custom of bleeding pregnant women is accepted with reservations. Nevertheless he cites a case in which a woman was bled 90 times in one pregnancy without apparent harm.

From Mauriceau we jump to the beginning of the nineteenth century for other evidence of special interest in prenatal care. In preparing this paper I glanced through the Catalogue of the Surgeon General's Library and was amazed to find record of no less than 55 dissertations written by graduates of French universities from 1800 to 1840 on the "Hygiene of Pregnant Women." I contrived to read about twenty of these dissertations. As a whole they do not display any great originality, and the manner of treatment is rather stilted; but their number is certainly evidence that French obstetricians of that period were keenly alive to the importance of giving prenatal instructions to pregnant women. There is a good deal of common-sense advice in some of these dissertations and a few examples may be of interest. Leglay writes (1812): "Have indulgence for the pregnant woman's caprices, listen to her desires with complaisance, console her and in place of the severity of the doctor, adopt rather the affectionate tone of a friend or a father." "Walking is the best form of exercise," says Nolette, "but it should be done in moderation and not transformed into a task or it will lose its advantage. Rather should the path of her promenade have pleasant surroundings and be made with good friends whose conversation may have so much charm that she will forget what was the purpose of her

walking.'' Ledesert warns against listening to the stories of gossips and matrons concerning the terrible experiences of other women in labor.

Venesection was accepted as a routine procedure during pregnancy among French obstetricians of this period. The problem was how often it should be done, at what period, from what extremity the blood should be taken and in what amount. It is interesting that at this same time German writers (Busch, Boer, Jörg, Naegele) were almost a unit in pointing out the dangers of routine venesection. Their instructions for the care of pregnant women do not otherwise differ materially from those already described.

In England, Denman (1801) warns against partaking of animal food in pregnancy. Women at this period usually prefer vegetables, fruit, and everything cooling. Concerning purgation he writes: ''The more gentle the means for the removal of costiveness, the more eligible they are, provided they answer the intention.'' He warns against the use of opiates for insomnia. A glass of cold water at bedtime will often suffice.

American obstetricians of the nineteenth century made a few valuable additions to prenatal care. W. Tyler Smith (1849) urges dental hygiene in pregnancy to prevent complications that may lead to abortion. Hodge stresses psychic management. The expectant mother should indulge in suitable reading and cheerful conversation, keeping away all stories relating to the complications of labor in other women.

Before considering present conditions among civilized peoples, a few examples of the customs among savage races might be of interest. Superstitions of all sorts are deep-rooted. Evil spirits are believed to be the cause of fetal death and abortion. Yawning is very dangerous, for the demon seizes this opportunity to jump into the body and kill the child. Beware of walking in the moonlight, as there are devils about! Pregnant women are sequestered in special houses away from harmful influences and in one tribe a bell is placed on the ankles of pregnant women so that the tinkling sound will warn others to keep away. In South America the natives do not eat lamb for fear of giving their child a stub nose. Salty or greasy food is declared harmful and a diet limited to cocoanut milk is advised in the last months.

Numberless examples are related of maternal impressions. In fact this subject has been ardently discussed pro and con all through the ages up to the present time. The Greeks and early Christians considered that beautiful children were the result of gazing at beautiful objects in pregnancy. From Utrecht comes a yarn related by Schwammerdam in 1672 of a woman who while pregnant saw a Moor, and to avoid having a black child quickly washed herself with warm water. The child at birth was white except between the toes and fingers, spots untouched by her ablutions. Birth marks were often produced because certain foods had been denied the pregnant woman. Against the views

of the majority occasional voices were raised. Colombo of Cremona in 1559 declared that monstrosities were not due to the devil or to sodomy but were the result of faulty development. A cogent argument against maternal impressions according to Blondel in 1727 was the fact that illegitimate mothers could not destroy their offspring by their most intense wishing.

Belief in the mysterious influence of mind over matter has come down to the present generation, and we find one of our founders, the first president of this society, Fordyce Barker, a convinced advocate of the doctrine of maternal impressions. At the meeting of the American Gynecological Society in 1886 he reported several instances of deformities produced in this way. In the discussion that followed Busey narrated 41 additional cases. Only one man raised his voice in opposition, John S. Billings, who said that such effects ran counter to all our knowledge of the physiology of pregnancy and hence we must simply say: "we do not know." A resolution was passed to have the question investigated by a special committee of three but our transactions do not record the report of that committee. Hirst's *Obstetrics* in 1888 stated that maternal impressions were a proved fact and even as late as 1902 Dickinson-Norris' textbook conceded them as a probability. The studies on pathologic embryology by Mall and Streeter have now shown the fallacy of these theories and point the way to methods of prevention.

The most important chapter in this story of prenatal care deals with the prevention of eclampsia and its associated toxemia. Previous to the middle of the nineteenth century the diagnosis and prevention of impending eclampsia was based wholly on clinical observations. Textbooks are full of accurate descriptions, vividly portrayed, of the premonitory symptoms. Dewees relates of a rapidly fatal case in which the patient suddenly cried out: "My head! My head!" and fell into convulsions. Epigastric pain, tingling of the ears, blind spots, and edema of the face and hands were evidence of plethora, and bleeding would alone prevent the eclamptic outburst.

It was in 1843 that J. C. Lever in England first noted the constant presence of albumin in the urine of patients with eclampsia or preeclamptic symptoms. At about the same time in France, Rayer, followed by Blot, Labat and Mayer Cahen noted the constancy of these findings. It was not long until the urine of every patient with edema or headache was examined and the appropriate treatment instituted where albumin was found. James Simpson of Edinburgh confirmed the uniform presence of albuminuria in eclamptic patients and in 1859 concluded that "albuminuria, dropsy, and convulsions are successive effects of one common central cause—viz, a pathologic state of the blood, to the occurrence of which pregnancy in some way peculiarly predisposes."

In Germany autopsy findings on eclamptic patients demonstrated the consistency of kidney pathology in these cases.

It was an accident of economic circumstances that led to the establishment by E. B. Sinclair and G. Johnston of the first prenatal clinic in the world at the Dublin Maternity Hospital in 1858. Owing to the crowded condition of the hospital, applicants for maternity care had to present themselves for admission several months before their expected confinement. Their card had to be signed by one of the physicians of the hospital, who took this occasion to make a brief record and physical examination. Every woman with edema, headache, dizziness, or albuminuria was treated actively. She was instructed to attend the dispensary regularly, and, if necessary, was admitted into the chronic patient's wards of the hospital. Here she was purged freely and repeatedly, made to maintain a horizontal position in a cool ward, and allowed none but the mildest and lightest nourishment. Sinclair and Johnston found that by these measures the incidence of eclampsia was greatly reduced. In fact almost the only patients with eclampsia were untreated emergencies who had not come to the dispensary.

The next important advance was the discovery of blood pressure elevation in eclampsia. It was a lapse of almost half a century from the first mercury manometer used by Ludwig in his animal experimentation, to the air-inflated sphygmomanometer of Potain in 1888. Working with the latter instrument Vinay in 1894 noted the regular occurrence of a high systolic blood pressure up to 180 to 200 mm. of mercury in women with eclampsia. Three years later Vaquez and Nobecourt amplified these findings and found that they preceded the convulsive seizures. At the German Gynecologic Congress at Giessen, in 1901, Füth and Kroenig reported a uniformly high blood pressure in preeclamptic patients. In the same paper they also showed certain differences in the freezing point determinations of the maternal and fetal blood. In the discussion that followed, the question of freezing point was carefully considered but the value of their blood pressure findings was completely overlooked.

At Johns Hopkins University in 1903, H. W. Cook and J. B. Briggs made careful studies of blood pressure after operations, during normal pregnancy and in eclampsia. Their conclusions were: "It is especially with regard to the early recognition of the onset of eclamptic features in any case and the possibility of instituting prompt and vigorous treatment for their relief that systematic blood pressure records may be of value to the obstetrician. The onset of hypertension at any period of pregnancy should always excite the apprehension of eclampsia in the absence of other recognized causes of abnormally high blood pressure."

Although this paper was published in the Johns Hopkins Hospital Reports in 1903, neither it nor the preceding European reports were mentioned in the symposium on eclampsia held by our Society two years later. Even in 1910 and 1912 when we again discussed this sub-

ject, only Hirst and Polak stressed the usefulness of blood pressure readings. In Europe, in spite of additional work by Vaquez, Wienner and others, the compendious *Handbuch* of von Winckel in 1907 fails to recognize the value of blood pressure measurements in eclampsia. It was not in fact until twenty years after Vinay's first work that the true significance of these findings was generally appreciated.

The establishment of special clinics for prenatal care on a nation-wide scale under university, hospital, or municipal administration dates back to the beginning of this century. Previous to 1900 we had only one such clinic, that already mentioned at the Dublin Maternity established in 1858. The man who first visualized the possibilities of prenatal care thus organized under hospital supervision was James Ballantyne of Edinburgh. Influenced by many years of study in antenatal pathology, he urged the establishment of a prematernity ward for the care and study of pregnancy complications. By dint of persistence the one bed provided at the Royal Maternity Hospital in 1901 for these investigations grew to a 23-bed ward two decades later. Ballantyne in addition to being a great scientist and clinician had in him the strain of a visionary. The dawn of the twentieth century found his spirits rising with the hope of an age when all expectant mothers would be properly cared for. In fantastic mood he pictures the perfect prematernity institution of the future. It is situated in the town of Weissnichtstadt, somewhere on neutral ground between France and Germany, built by the munificence of an American millionaire, and officered by an international staff. Over the doorway runs the legend: "Teach us what we shall do unto the child that shall be born." In one ward abortions and premature labors are being prevented. In another, the so-called "hall of the innocents," syphilis in the pregnant mother is being eradicated. The room whose doorway is labeled "Heredity" contains a hemophiliac who is being cured by some new method. In the Roentgen room the art of prenatal diagnosis is being perfected. Many of these dreams of Ballantyne have indeed come to pass. Only the concluding remarks of the physician-in-charge sound strangely incongruous at the present time. Ballantyne puts these words into his mouth: "In this twentieth century we prevent everything—war, disease, hurricanes—everything except the doing of good to others." We are thankful that Ballantyne did not live to see how far this Utopian vision is from being fulfilled.

In England the movement for prenatal care was greatly aided by the National Health Insurance acts of 1911 and 1913, providing for maternity benefits. In 1914 the local Government Board issued a circular offering a grant to local authorities for antenatal care. This included: (1) local supervision of midwives, (2) antenatal clinics, (3) home visiting of expectant mothers, (4) provision in hospitals for treatment of the complications of pregnancy. By 1927 there were already in existence 600 prenatal clinics in England alone.

In the fully organized obstetrical services of the Scandinavian countries and Holland the establishment of proper prenatal care through midwives and physicians was relatively simple. In Holland according to Dr. DeSnoo the work has been done individually with each patient through the person in attendance, rather than through a general prenatal clinic as elsewhere. Soviet Russia has devoted special consideration to the care of the expectant mother. On a nationwide scale it has established centers for maternal welfare where patients are instructed and examined. This is one of the big accomplishments of the present government.

In France Pinard led the movement for prenatal care. The interruptions of the Great War were partly compensated by the splendid cooperation of American physicians at the time of its conclusion in 1918. Dr. Fred Adair was in charge of a portion of this prenatal work during these years and the experiences gained there stood him in good stead when he took over the chairmanship of the Committee on Maternal Welfare in this country. This committee's activities were the indirect outgrowth of the Conference on the Prevention of Infant Mortality held at New Haven in 1909. The work progressed rapidly and by 1915 Whitridge Williams prepared a model prenatal record sheet. "The best results in prenatal care are obtained," he says, "when work is begun in the obstetric dispensary of a well-regulated hospital, continued in the lying-in wards and completed by the children's hospital with its milk fund and baby saving devices."

In 1920 a committee of three was appointed by the American Gynecological Society to confer with similar committees appointed by the American Pediatric Society and the American Child Health Association to plan for the development of a maternal and child welfare program in the United States. The splendid work of this committee and its successors is too recent to need amplification here. Its influence was made nationwide by the publicity and the illuminating studies that grew out of the White House Conference of 1931, studies in which the Fellows of our Society took a distinguished part.

At the present time I think it is not an idle boast that in spite of the handicaps arising from our vast territory, the admixture of various races, especially negroes, and the heterodox requirements for medical practice, we have succeeded in this country in developing one of the best organized systems for prenatal care in the world. It is a chapter in our obstetric development of which we have reason to be proud.

Such in brief is the history of prenatal care. In conclusion may I recall to your mind one episode from this record that should have a special significance for us at the present time. I refer to the discovery of blood pressure elevation as an index of threatened convulsions. In 1905 the Fellows of our Society gathered for a symposium on eclampsia.

French and German medical journals had for ten years previously contained important contributions on the subject of hypertension in eclampsia. In our own country Cook and Briggs had made careful observations on high blood pressure associated with eclampsia as early as 1903. Yet by no word or suggestion was this fundamental advance recognized in our discussion of the subject. I bring this up not in a spirit of criticism but to ask you here today to consider whether we may not in similar manner be overlooking discoveries, already made, but whose value we have not fully recognized. As Fellows of this Society, is it not our responsibility, not merely to add to the sum-total of scientific knowledge by our own investigations, but also to develop our critical faculties, so that we may become discerners of the truth, able to pick the grain from the chaff, and ever alert to recognize great discoveries promptly when they are made? By so doing, we shall materially hasten the progress of medicine.

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SARCOMA OF THE UTERUS*

Clinical and Pathologic Study of Fifty-Nine Cases

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SARCOMA of the uterus is so much less common than carcinoma of the same organ that it is not surprising that it has received far less attention in the literature. Most of the publications on the subject have dealt with reports of single cases or small groups of cases, as might perhaps be expected from the paucity of material in any but the larger clinics and laboratories. Our knowledge of many of the features of uterine sarcoma is still very incomplete, though it has been recognized as a clinical and pathologic entity since 1860, when the first case was reported to the Berlin Obstetrical Society by C. Meyer. No less a personage than Rudolf Virchow made the pathologic report on this case, and an accurate description of uterine sarcoma of the endometrial type was incorporated in his *Krankhafte Geschwülste*, published in 1865. In the seventy-seven years since Meyer's report only a relatively small group of contributions may be said to have represented serious efforts to add to our knowledge of this subject.

It has therefore seemed worthwhile to study the comparatively large material which has passed through our laboratory, the present report covering a period of twenty-five years (1911-1935 inclusive). During this time, in a total of 26,973 case specimens, 59 cases of uterine sarcoma have been encountered. These have been studied from both a clinical and a pathologic standpoint, for only by such a correlation can one expect to extract the fullest information as to the characteristics of this disease. We have been fortunate in having follow-up information on 50 of our 59 cases, in spite of the fact that 18 specimens or sections came to our laboratory from outside clinics, meaning usually considerable difficulty in getting information as to the postoperative careers of the patients.

In an excellent paper before this Society in 1934, Kimbrough presented an analysis of 43 cases of sarcoma of the uterus, more especially from the standpoint of the factors which influence the end-results. The reader may be referred to this paper for a résumé of the literature on this and other clinical aspects of the problem. While in our present paper we have likewise included an analysis of the clinical characteris-

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ties and end-results in our series of cases, we have been perhaps even more interested in the pathologic study of the rather large material at our disposal.

Table I will give some idea of the incidence of sarcoma of the uterus as compared with the other more common uterine lesions encountered in the twenty-five year period under study.

TABLE I. RELATIVE INCIDENCE OF UTERINE SARCOMA AS COMPARED WITH MORE COMMON UTERINE LESIONS OBSERVED IN 26,973 CASE SPECIMENS

DIAGNOSIS	NUMBER OF PATIENTS	INCIDENCE PER CENT
Myoma uteri	6,981	25.9
Adenocarcinoma of fundus	241	0.89
Adenocarcinoma of cervix	88	0.33
Epidermoid carcinoma of cervix	934	3.5
Sarcoma of uterus	59	0.22

Sarcomas, therefore, constituted 4.5 per cent of uterine malignancies (exclusive of chorionepithelioma) encountered during this quarter of a century. If the 18 patients treated in other hospitals be excluded, the incidence of sarcoma of the uterus was 0.15 per cent, and this tumor accounted for 3.1 per cent of uterine malignancies (exclusive of chorionepithelioma). In Kimbrough's investigation, sarcoma constituted 3.2 per cent of uterine malignancies, while Haase found the proportion to be 3.3 per cent, a rather remarkable uniformity in these three large groups of cases.

Clinical Characteristics.—The disease most frequently affects women during the middle period of life, our own series showing the highest incidence during the fifth decade. On the other hand, the rare grape-like sarcoma of the cervix occurs often in infancy.

TABLE II. AGE INCIDENCE

AGE	NUMBER OF PATIENTS	INCIDENCE PER CENT
7 months	1	1.8
2 years	1	1.8
14 years	1	1.8
20-25 years	2	3.5
26-30 years	4	7.0
31-35 years	6	10.5
36-40 years	6	10.5
41-45 years	10	17.5
46-50 years	10	17.5
51-55 years	4	7.0
56-60 years	8	14.0
61-65 years	3	5.3
66-70 years	1	1.8

Any portion of the uterus may be the seat of the tumor, though the body is far more frequently involved than is the cervix. Piquand, for example, found in a collective study of 393 cases that the body of the uterus was involved in 325 and the cervix in 68. The greater frequency

of corporeal as compared with cervical myomas will no doubt explain in part at least the predilection of sarcoma for the corpus uteri.

The symptomatology is not distinctive, so that in most cases the diagnosis is not made until operation; or even more frequently, not until the pathologic examination. Abnormal bleeding may be entirely absent, especially when the endometrium is not involved. On the other hand it may be of great significance, especially when it occurs after the menopause, and particularly when in these postmenopausal cases the uterus is the seat of myomatous growths. In younger women there may be either menstrual excess or intermenstrual bleeding, or both. Needless to say the hemorrhage is in any event only suggestive of possible malignancy, and carcinoma will more frequently be found to be its cause than sarcoma.

Abnormal discharge may likewise be a symptom, as in carcinoma. In earlier stages it is likely to be thin and watery, but sooner or later serosanguinolent. Still later it may, as a result of necrosis and ulceration, become quite foul, and may even contain sloughing particles or shreds of tissue. Rapid increase in the size of myomatous tumors, especially when this is associated with bleeding, should likewise suggest the possibility of sarcoma. Pain may be a symptom, though often not until the later infiltrative stages of the disease, when it may be intense and continuous. In these late stages, profound anemia, cachexia and weakness may be noted, making these patients very unfavorable risks for operation. Indeed, one must be struck with the number of patients, in both our own series and that of Kimbrough, in which death occurred within the first few days after operation, throwing into doubt the advisability of operation in such advanced cases.

Still other symptoms, none of them distinctive, may be noted, as will appear from Table III. In some cases diagnostic curettage will establish the diagnosis, as where the disease is polypoid or where the endometrial surface is involved, but when the disease is beneath the surface, microscopic examination of curettings will not be helpful.

TABLE III. SYMPTOMS

SYMPTOMS	NUMBER OF PATIENTS IN 57 CASES
Irregular bleeding	37
Pain, abdominal and pelvic	27
Tumor, abdominal and vaginal	24
Loss of weight	7
Foul, nonhemorrhagic discharge	4
Frequency of micturition	4
Painful defecation	2
General weakness	2
Dysmenorrhea	1

Extension of the disease is by direct continuity, by the blood stream, or by the lymphatics. The hematogenous route is most important in

metastasis, which therefore is more characteristically systemic rather than regional. Among the organs, most frequently the seat of these metastases, are the lungs and liver. In 33 autopsy cases Gessner found metastases in 24, including 15 in the lung, 10 in the liver, 8 in the intestine, 5 in the omentum, 5 in the kidney, 5 in the pleura, with smaller numbers in other organs, such as the brain, ovaries, heart, etc.

Other clinical data from our own cases are briefly summarized, without further comment, under the following heads: Race, age of puberty, familial incidence of malignant disease, and social status.

RACE

The race of the patient was known in 56 instances. Of these cases of sarcoma of the uterus, 53.6 per cent occurred among white patients and 46.4 per cent among colored women.

Age of Puberty.—Information regarding the menarche could be obtained in only 48 cases, and even at the best this is likely to be lacking in accuracy. In 60.5 per cent of these cases the age of puberty was between twelve and fourteen years.

TABLE IV

AGE	NUMBER OF PATIENTS	INCIDENCE PER CENT
9 years	1	2.1
11 years	4	8.3
12 years	13	27.1
13 years	8	16.7
14 years	8	16.7
15 years	7	14.6
16 years	5	10.4
17 years	1	2.1
18 years	1	2.1

Familial Incidence of Malignant Disease—Investigation of the family history in 56 cases of sarcoma of the uterus showed that there was no incidence of malignant disease in 53 or 94.6 per cent, while positive evidence was noted in 3 or 5.4 per cent.

TABLE V. SOCIAL STATUS

STATUS	NUMBER OF PATIENTS	PER CENT
Unmarried	5	9.1
Unmarried with pregnancy	1	1.8
Married without pregnancy	6	10.9
Married with pregnancy	43	78.2

"Recurrent Fibroids."—In the older literature one finds frequent reference to "recurrent fibroids" and to malignant myomas with the capacity to recur and to metastasize. There can be little doubt that these growths were really types of sarcoma, and yet in a number of reported cases, vagaries of behavior have been described which are difficult of explanation on general pathologic grounds. In a case reported from Halban's clinic by Christophorakos, recurrence occurred

one and a half years after hysterectomy for a myoma in which there was a "suspicion of sarcoma." The histologic examination of the recurrent tumor, however, failed to show any evidence of malignancy, though blocks were made in from 20 to 25 different areas. A third operation was done ten months later for a second recurrence and again the tumor proved to be a myoma with no suspicion of malignant change. Six months later a retroperitoneal recurrence appeared and the examination of this showed areas of polymorphic sarcoma in addition to myomatous elements. The patient died two years later. Neugebauer has also reported a case in which, six years after supravaginal hysterectomy for benign myoma, there were found 3 pelvic tumors entirely separated from the amputation area and all showing the histologic structures of simple benign myoma.

Pathology and Classification.—Much of the older discussion concerning the pathology of sarcoma of the uterus has revolved about the problem of its histogenesis, and more particularly about the question as to whether the sarcoma may arise directly from muscle cells or whether it has its source always in connective tissue elements. Without going into the history of this controversy, suffice it to say that the former of these viewpoints is now the accepted one. As far back as 1894, Williams demonstrated what he considered a direct transition of muscle cells into sarcoma cells, and Kelly and Cullen, as well as other authors, made similar observations. In more recent years there has been much discussion as to whether sarcoma can arise from the mature muscle cells of the uterine wall or of a myoma, or whether it must spring from rests of undifferentiated cells which persist in the uterine wall. Merely to summarize the existing evidence, the majority of leading pathologists agree with Meyer that an origin from fully differentiated muscle cells is unproved and unlikely. This, after all, is the same problem which exists as regards sarcoma and other malignant growths in other parts of the body, with the same preponderance of opinion as to the improbability of the fully differentiated cell being the source of the malignant cell elements.

To hark back for a moment to the question of whether muscle or connective tissue cells are primarily concerned in the histogenesis of sarcoma, it must be remembered that all the constituent elements of the uterus—muscle, connective tissue, epithelium, blood vessels—are of common embryonic ancestry, and all are of mesodermal origin. It would, therefore, be surprising if a malignant connective tissue tumor-like sarcoma could not arise from any one of these elements, or, for that matter, if at times a mixed tumor could not likewise develop, as is actually the case. This, as a matter of fact, represents the preponderant view of leading authorities as to the histogenesis of uterine sarcoma. It may arise from the muscle cells of the uterine wall or of uterine

myomas, or from the connective tissue elements in the uterine wall, or in myomas, or in the endometrium, or from the walls of the blood vessels of the uterus.

It is on these grounds that we base the usual classification of sarcomas into (1) those arising in the muscle or connective tissue of the uterine wall, (2) those arising in myomas of either the corpus or cervix, (3) those arising in the mucous membrane of either the corpus or cervix, (4) those arising in the blood vessel apparatus. An origin from any of these sources is possible and in individual cases has been demonstrated, but, unfortunately, in a very large proportion of cases which come to study, it is not possible to do more than conjecture as to the origin, and in many cases even conjectures seem hopeless. No matter

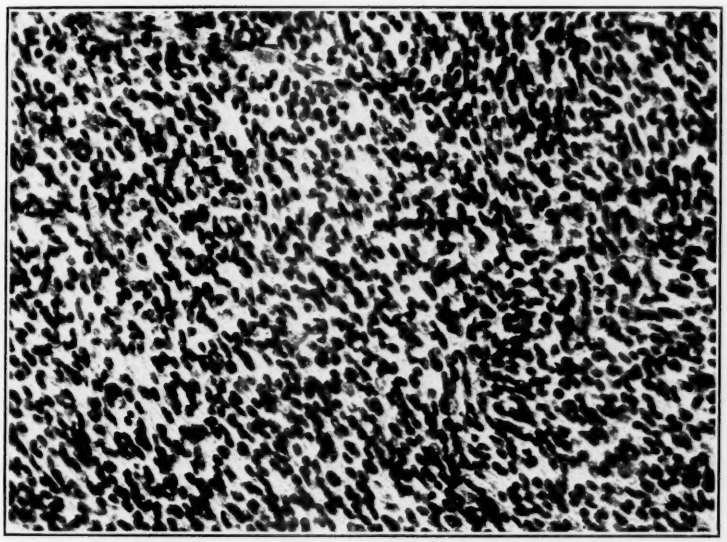

Fig. 1.—Sarcoma of dominantly small spindle cell type in patient of sixty-five years, reported well several years after operation.

what the origin, the invasive tendencies of sarcoma tend soon to blot out the evidence for this, and morphologic differences are all too often insufficient to establish the histogenesis of many advanced cases.

The uncertainties in classifying many cases, together with the rather limited practical value of such classifications, make it seem more important, with some reservations as regards special types, to lay more stress upon classifications dependent on cell type and degree of cell differentiation, because of the conceded importance of such variations as indicators of the relative malignancy of tumors in general.

It seems to us, therefore, that the time-honored division of sarcomas into the spindle cell (Fig. 1), round cell (Fig. 2), and mixed cell groups is as serviceable as any in the classification of uterine sarcoma. To these we might add a giant cell variety. Refinements of this classifica-

tion, with the use of terms which aim at greater descriptive precision as to the constituent cells and their probable histogenesis, have been suggested, but they are of more value in the hands of experts than in those of the average pathologist. For example, such terms as sarcoma myoglobicellulare, sarcoma myofusicellulare, and sarcoma myocellulare are employed by Meyer in the grouping of myogenic sarcoma on the basis of histogenesis and degree of cell maturity.

All such classifications, however, have the weakness that in an evitable and not small proportion of cases the pathologist cannot be sure of the exact histogenesis. Moreover, in this method of classification, as well as in the simpler one more generally employed, viz., into round, spindle or mixed cell types, one cannot eliminate the individual factor in inter-

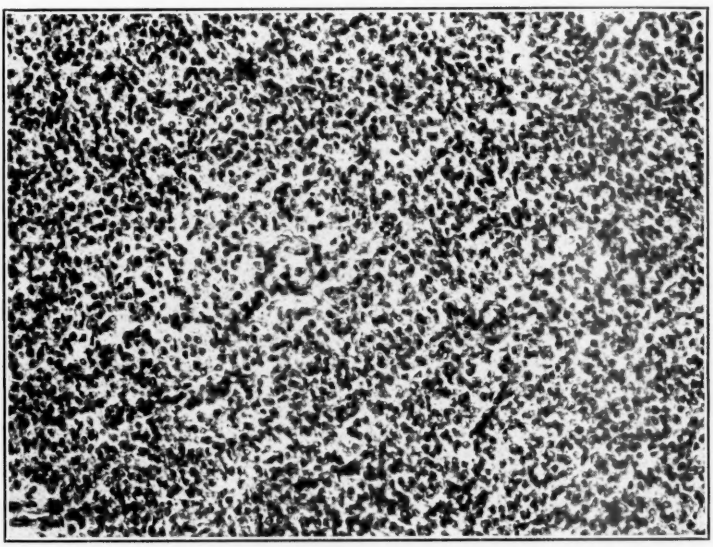

Fig. 2.—Round cell sarcoma in patient of forty-nine years, well eighteen years after operation, followed by radiation.

pretation. For example, in the spindle cell variety many of the cell bundles are cut transversely, producing a round cell picture in such areas, and leading often to the diagnosis of mixed cell sarcoma. To obviate this, Meyer makes the useful suggestion that the course of the blood vessels may serve as a valuable guide. If for instance, in an area in which blood vessels are observed in longitudinal section, the cell type is round, the diagnosis of round cell sarcoma would be justified, whereas round cell areas without such histologic control might well be cross-sections of spindle cells. Even with allowance for such factors, however, there is no doubt that the cell type in different tumors and even in different parts of the same tumor may show all grades of dedifferentiation, from a very immature type of round cell to a fusiform

cell scarcely distinguishable from the normal. The round cell variety is relatively rare as compared with the spindle or mixed cell type.

The *gross characteristics* of sarcoma of the uterus show great variation, depending especially upon histogenesis and location. In the most frequent type, that arising in uterine myoma, the sarcomatous change often brings about a sufficiently definite macroscopic alteration to justify a presumptive diagnosis of sarcoma; in others the change is much less marked, so that sarcoma will not be suspected until microscopic examination. The sarcoma areas occur most frequently near the center of myomas, but may at times be noted only in the periphery. Instead of the hard rather glistening cut surface of a typical myoma, with its characteristic whorl-like appearance, the sarcoma areas present either the "raw-pork" appearance described by Cullen, or, when necrotic changes are more marked, they present as brain-like pultaceous, broken-down areas, with often a ragged cavity formation and perhaps hemorrhage. The common hyaline degeneration of benign myomas may at times lead to confusion, as it may bring about rather large areas of amorphous appearance, in which the characteristic architecture of myoma is likewise lost. However, the consistency is likely to be firmer than that of sarcoma unless there is also present the easily recognizable cystic degeneration.

Mural sarcomas may at times also arise as nodular and fairly circumscribed tumors, so that it may be difficult to be sure whether or not the tumor was preceded by a benign myoma. More often, however, they are much more diffuse in their growth, so much so that they may produce a fairly uniform enlargement of the uterus, which may even resemble an early pregnancy. The same thing is true of the diffuse varieties arising from the endometrial stroma.

The endometrial sarcoma not infrequently assumes a polypoid architecture, and this is likewise true of growths originating from the mucosa of the cervix. As a matter of fact, the superficial cervical sarcomas may be mistaken for benign polyps, as in one of our own cases, in which sarcoma was not suspected before microscopic examination. As a rule, however, the polyps are bulkier, denser, and more friable than the common benign variety. In other cervical sarcomas, there may be widespread ulceration and infiltration, producing a picture not distinguishable from the far more common carcinoma in its advanced stages.

Finally, a word as to the rare grapelike sarcoma of the cervix (sarcoma botryoides), particularly as our series includes two specimens of this lesion. This grapelike tumor (traubiges Sarcom) was described by Spiegelberg as far back as 1897, under the designation "sarcoma colli uteri hydropicum papillare," and various other names have been applied to it by other authors. From a clinical viewpoint, the most interesting feature of this disease is that while it may occur in adults it has often been noted in infants, and this age predilection would sug-

gest a special histogenesis, for which opinion there is histologic support. This grapelike sarcoma presents as a grapelike mass of pinkish, edematous polyps involving the cervix and usually also the upper vagina. In advanced cases the entire vaginal canal may be filled, with widespread lateral infiltration of the whole pelvis. The disease is always fatal. Of especial interest, however, is the fact that among the sarcomatous elements one may find also other mesodermal elements, especially embryonic striped muscle, with, less frequently, cartilage.

While mixed tumors of the uterine body also occur, this teratoma-like mixture is much more frequent in the small cervical group of botryoid tumors, lending support to the theory that they are of teratoid nature. Because of the rarity of these tumors, a brief report of the two cases in our present series seems justified.

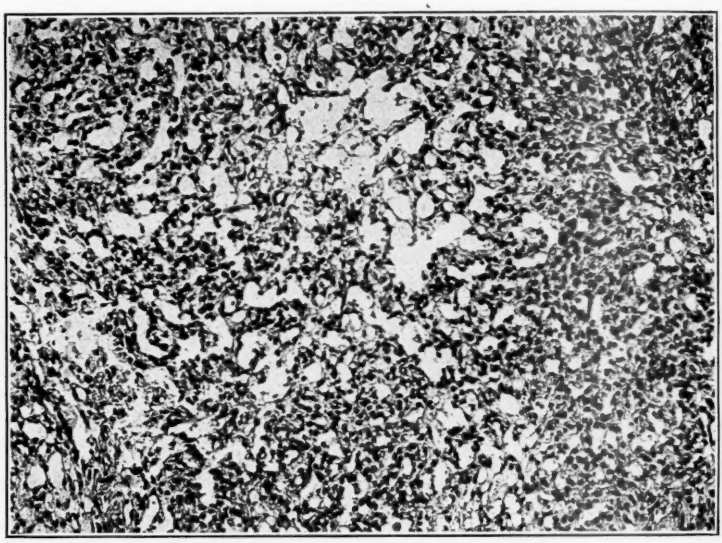

Fig. 3.—Sarcoma botryoides (kindness of Dr. José Medina, Sao Paulo) in infant of seven months.

CASE 1.—This specimen was sent to one of us (Novak) for pathologic examination by Dr. José Medina, of Sao Paulo, Brazil. It was obtained by biopsy from a polypoid tumor which filled the vaginal fornix, presumably arising from the cervix. The patient was an infant of seven months. The tumor was described as friable and very vascular. The child died, but autopsy was not obtainable.

The histologic examination, as will be seen from Fig. 3, shows the tumor to be made up of cells chiefly of spindle type, arranged for the most part around small spaces which are evidently lymph channels. The cells themselves show only a rather low degree of anaplastic change, though many of the nuclei are rather large and heavily stained. There is no evidence of unstriped muscle or of other teratoid elements. The more superficial parts of the tumor show extensive necrosis and inflammatory infiltration.

CASE 2.—The patient was a child of two, who for six months had had vaginal bleeding, with the occasional passage of small polypoid masses from the vagina.

The cervix is said to have been amputated at another hospital some time previously, and she had had two radium treatments (dosage not known). She had, however, become progressively worse, with the development of cachexia, together with a severe pyelitis. The tissue which came to our laboratory, through the kindness of Dr. Margaret Handy, of Wilmington, Delaware, consisted of two small polypoid masses expelled from the patient's vagina and showing typical sarcoma (Fig. 4). The case terminated fatally a short time later.

A third case, representing a cervical polypoid sarcoma in an adult, was not of the typical botryoid variety, but it is of sufficient interest to justify brief mention.

CASE 3.—This case we are permitted to include in our series through the kindness of Dr. Karl M. Wilson, Professor of Obstetrics and Gynecology at the University of Rochester School of Medicine and Dentistry, who was good enough to send us slides for examination. This patient was thirty-eight years old. Seven years previously she had been given x-ray treatments because of uterine bleeding, and

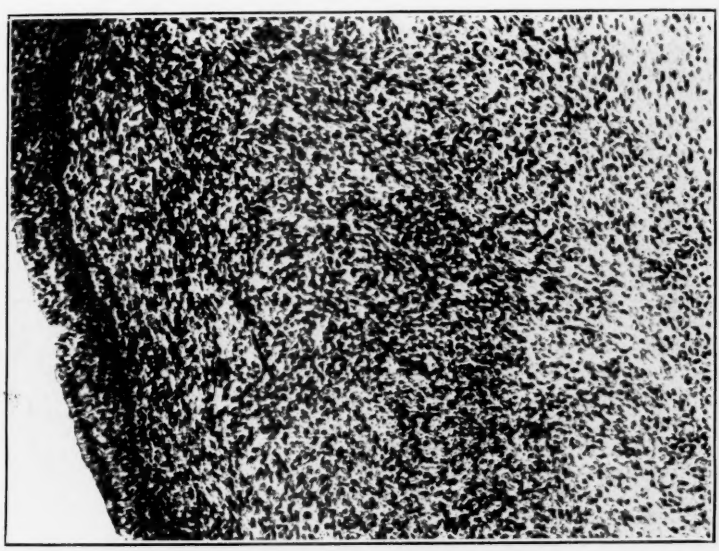

Fig. 4.—Sarcoma botryoides in child of two years. (Case of Dr. Margaret Handy, Wilmington, Del.)

complete amenorrhea had ensued. For two months before being seen, however, she had bled almost constantly. On examination a polypoid growth was found in the cervix. According to Dr. Wilson's note, "the growth bled on touch, presented a rather offensive odor, and suggested a necrosing polyp or a small submucous myoma." This was removed by the vaginal route.

The histologic examination shows a finely lobulated polypoid tumor which apparently arose from the cervix, as stratified squamous tissue covers the sarcoma in some places, while in others the small polyps are covered with cervical and even with endometrial epithelium. In the latter areas, the subepithelial cells resemble a highly active endometrial stroma, with numerous mitotic figures, often as many as six or eight in a high power field. In the lower portion of the growth (Fig. 5), where the covering epithelium is of the stratified squamous type, the cells are larger, spindle-shaped, with many giant nuclei, few mitoses, and extensive degeneration. The growth is evidently a polypoid cervical sarcoma of mucous membrane origin.

Microscopic Characteristics.—With reference to the microscopic appearance of uterine sarcoma, it is scarcely necessary to go into detail, inasmuch as the same wide variation in cell morphology occurs which characterizes sarcoma in general, and, as we have already mentioned, there may be much variation in different parts of the same tumor with regard to the degree of de-differentiation of the constituent cells. The pattern and architecture likewise present much individual variation, some growths being very cellular and diffuse, others having an alveolar or plexiform pattern (Fig. 6), while in rare cases the relation to the blood vessels justifies the designation of angiosarcoma (Fig. 7). The alveolar pattern seems in most cases to be imparted by the presence of subdividing masses of connective tissue usually showing extensive hyaline degeneration.

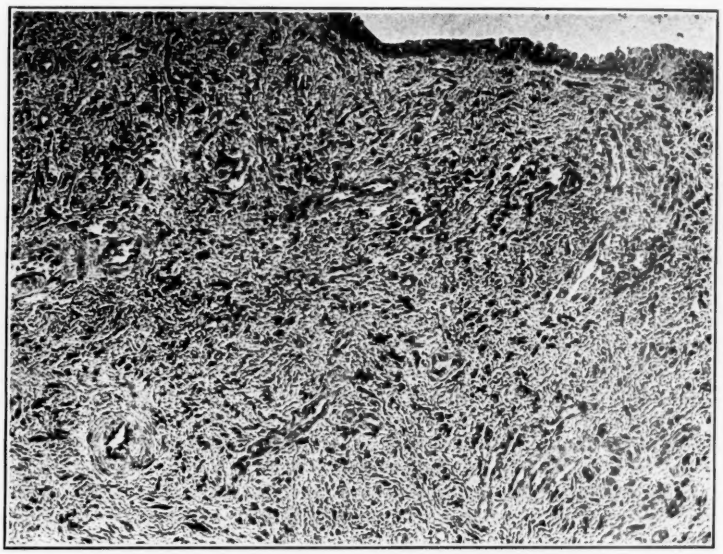

Fig. 5.—Polypoid cervical sarcoma in patient of thirty-eight years. (Kindness of Dr. Karl M. Wilson, Rochester, N. Y.)

In many myogenic tumors there appears to be an insensible transition from normal muscle cells to the malignant cells, and in some tumors the constituent cells show only mild degrees of departure from the mature muscle cells. In others, though the cells may still be definitely spindle-shaped, there is a marked degree of anaplasia, with much hyperchromatosis, frequent mitoses, and often giant cells.

The term giant cell sarcoma is often employed, but the significance of such elements is not always the same. In perhaps the majority of cases giant cells are found in tumor areas which are obviously degenerating, and it seems clear, from the study of transition stages, that the large giant cells, often polynuclear, are formed from the cytoplasmic confluence of degenerating sarcoma cells (Figs. 8 and 9). One usually

finds little evidence of nuclear activity in such areas, while in other parts of the same tumor the picture may be quite different, with marked anaplastic cell changes, many mitoses, and often no giant cells.

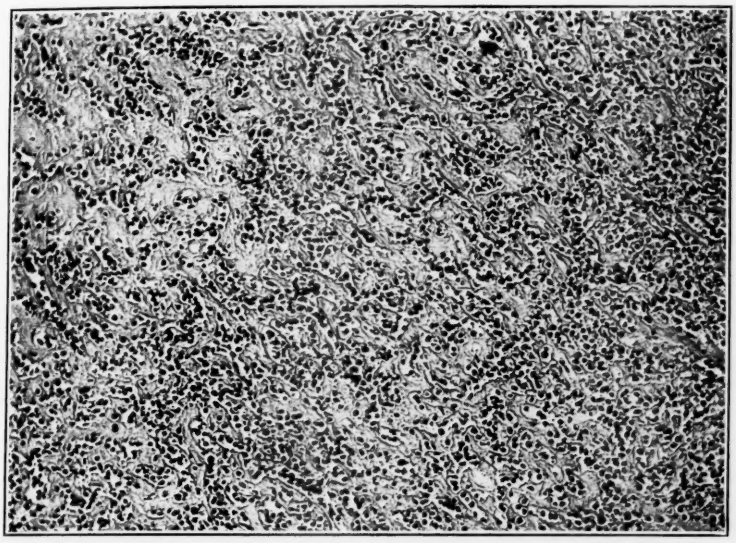

Fig. 6.—Sarcoma of alveolar pattern, with septa of hyalinized fibrous tissue dividing the tumor cells. Patient, aged forty-six years, living and well several years after operation.

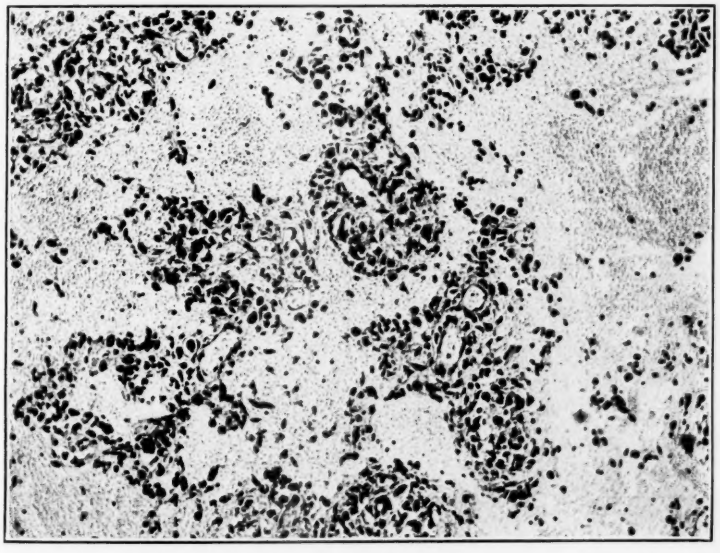

Fig. 7.—Angiosarcoma in patient of forty-two years. Growth far advanced, with loss of 110 pounds in weight, and death soon after operation.

There are, however, other cases in which the designation of giant cell tumors would seem more justifiable, because in these the large giant nuclei are sharply and intensely stained, evidencing a hyperchromatosis

which must be looked upon as an indication of abnormal cell activity (Fig. 10). Frequently, though not by any means always, such tumors also exhibit numerous mitoses.

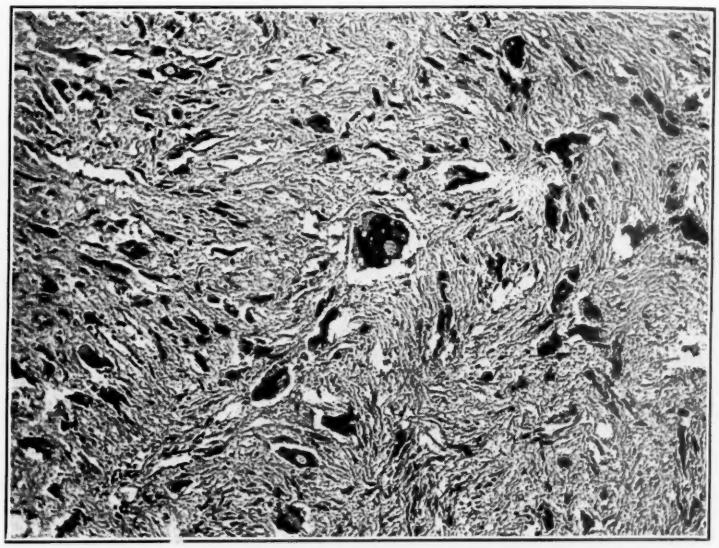

Fig. 8.—Giant cells of symplasmic type, due to degeneration process.

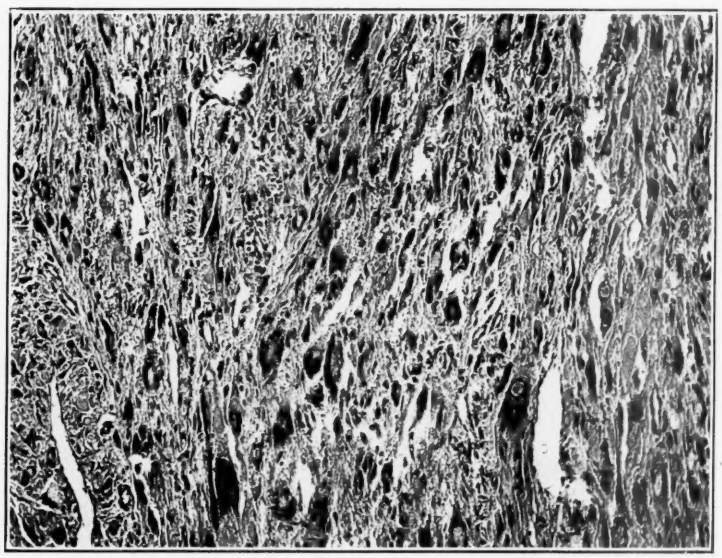

Fig. 9.—Degenerative type of giant cell formation.

As an important index of the degree of malignancy of uterine sarcomas, much stress has in recent years been put upon the nuclear behavior, and especially upon the relative number of mitoses which may be

present. It would seem quite certain, on general pathologic grounds, that this criterion is of importance.

In a paper published in 1919, Proper and Simpson suggested a classification into 3 types (I, II, III) according to the degree of maturity of the constituent cells. In their own cases the clinical malignancy seemed to parallel the degree of cell immaturity. For example, of their 11 cases of Type III, only 1 was well (though only six months had elapsed since the operation), 1 had a recurrence, 2 died soon after operation, and 7 died of recurrences in from six to eleven months after operation.

Renewed interest in the question of mitotic activity was awakened by the paper of Evans in 1920. In a study of "malignant myomas" he concluded that the degree of mitotic activity parallels the clinical

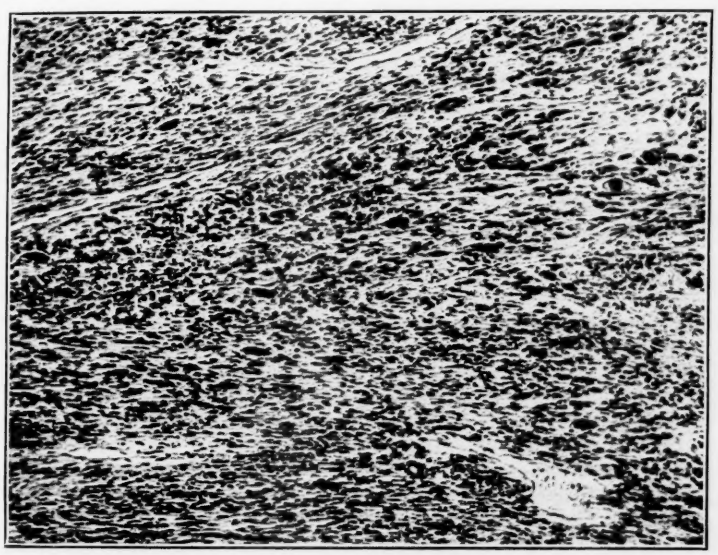

Fig. 10.—Giant cells in actively growing tumor of spindle cell type. Patient, aged sixty-six years, died on thirteenth postoperative day, of pyelonephritis.

malignancy of these tumors. He based his estimates of nuclear activity upon actual mitosis counts by a technique not unlike that employed in blood counts. It should be remembered, however, that such a method can be of considerable value only when the pathologic technique is a very standardized one. The rapidity of fixation, the thickness of the sections and other such factors are so variable in the average group of cases studied that there could be no mathematical accuracy in mitosis counts of this sort. This would apply to such a series of cases as ours, going back over twenty-five years and including many cases from outside sources. It would seem to be just as serviceable and perhaps approximately as accurate in giving an idea of the degree of nuclear activity to count the mitoses in a considerable number of fields from as many different parts of the tumor as possible. This is the plan which

we have adopted in our own study, 20 separate high power fields being counted for mitotic figures. We are inclined to believe that the results of this are not widely different from those which would be obtained had we employed the more intricate technique of counting suggested by Evans.

Mitosis counts were made in all our cases except those in which only one section was available, with too small an area of sarcoma to permit of the study of 20 suitable high power fields, and those where extensive degenerative changes would make mitosis studies valueless. In all, 41 of our cases lent themselves for study along these lines, yielding mitosis counts varying from 0 to 88 in 20 high power fields. As might be expected, and as both Evans and Kimbrough found, the degree of nuclear activity as indicated by the mitosis counts parallels in a general way the degree of clinical malignancy manifested by the tumor. Indeed, the parallelism is quite remarkable.

Of 20 cases in which from 0 to 5 mitoses (inclusive) were found in 20 fields, 15 were living more than three years after operation, 1 died of recurrence ten years after operation, 1 received only palliative treatment and presumably died, and 3 were not traceable. Of 4 patients with between 6 and 10 mitoses (inclusive), 2 were well and 2 died (seven months and five years after operation). Of 4 with between 11 and 20 mitoses, 1 died after ten years of an intercurrent disease, and the 3 remaining were dead, three weeks (sepsis), five weeks (sepsis), and seven months after operation. Of 6 patients with from 21 to 30 mitoses (inclusive), 1 was reported well six months after operation but has not been traceable since, 3 were dead (seventy-two hours, seven months, and seven years after operation), and 2 could not be traced. Finally, of 7 patients with mitosis counts above 30 (up to 88), 4 are known to have died (one day, seven months, 2 at nine months), and the remaining 3 presumably died soon after discharge from the hospital, for all 3 were far advanced, receiving only palliative treatment.

A fact which has interested us is that, with one or two exceptions, the patients with very low mitosis counts, in which recovery was the rule, were those in which the tumor developed in myomas, and in which it was of the spindle cell or mixed cell type, with few or no mitoses. This, fortunately, is the most common variety of sarcoma developing in myoma, and explains why so many cures have followed simple supravaginal hysterectomy, and why sarcoma recurrence is so rare after radiation treatment of myomas. In a minority of cases, however, myomas may be the origin of the more malignant types, though the latter are much more commonly seen when the tumor arises in the musculature or the mucous membrane of the uterus. To put it another way, sarcoma of the uterus may be either of a relatively low grade of malignancy or it may be of a very malignant type, and the proportion of the former is much greater among growths developing in myomas than in those developing in the uterine mucosa or musculature.

With reference to the much discussed question of the incidence of sarcomatous changes in myomas, the wide discrepancies of figures formerly quoted have given way to a reasonable degree of uniformity in more recent statistics based on a clearer recognition of the histologic criteria of malignancy. The most common mistake of the earlier authors was to mistake very cellular but benign myomas for spindle cell sarcoma, so that in some series an incidence of as much as 10 per cent of malignancy was reported (Werner). It is not always easy to be sure whether or not sarcoma is secondary to benign myoma. The mere presence of myomas does not justify this assumption, and, moreover, it must be remembered that sarcoma may arise as a rather nodular growth which might simulate a sarcomatous myoma. On the other hand, when a sarcoma is found developing in the interior of a myoma in which one

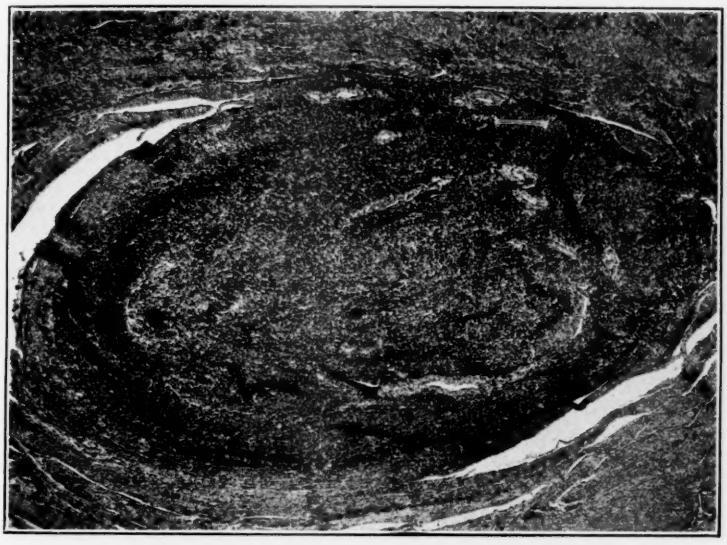

Fig. 11.—Sarcoma nodule developing in myoma. Patient, aged forty-seven years, has remained well after operation.

can still find abundant evidence of the original benign tumor, the origin from such a tumor seems clear (Fig. 11).

The same difficulties arise with reference to sarcoma arising in the mucous membrane. When one finds sarcomatous polyps of the endometrium or endocervix with little or no extension into the musculature, the mucous membrane origin must be accepted. Even in the more invasive types, where the muscularis is invaded, the replacement of the mucous membrane stroma by sarcoma cells, perhaps the presence of sarcomatous polyps, and the direct continuity of the sarcomatous stroma with the sarcomatous invasion of the muscle make the endometrial or endocervical origin reasonably certain (Figs. 12 and 13).

In the late stages of the disease, however, such aids in determining the origin of the tumor are not available, and one can only speculate on this

point. For this reason, we can claim no accuracy in our effort to classify our cases according to their origin; viz., (1) 39 in myomas; (2) 11 in the uterine wall; (3) 5 in the endometrium; and (4) 4 in the cervix.

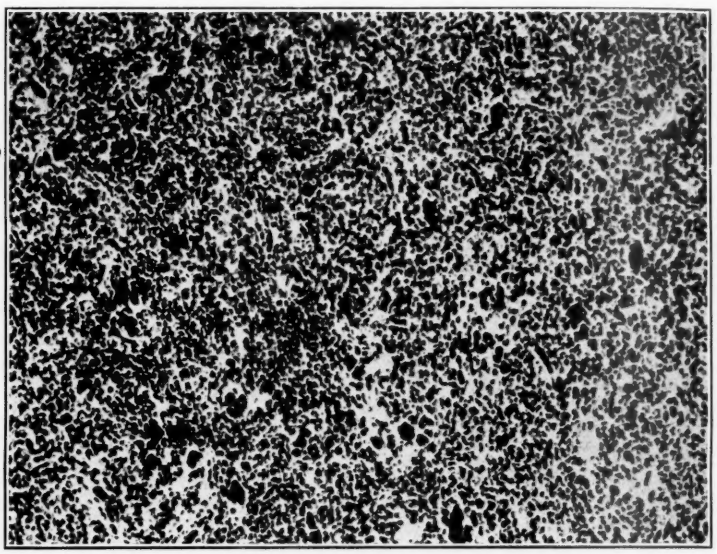

Fig. 12.—Endometrial sarcoma in patient of twenty-eight years of age, with death nine months after radical operation.

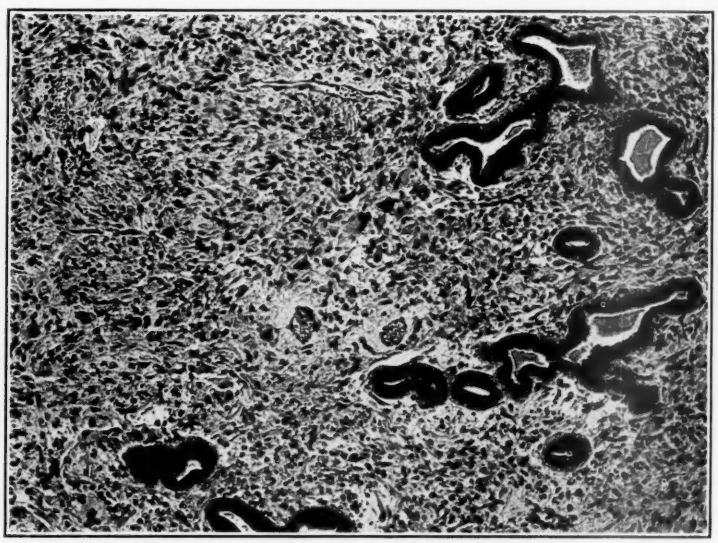

Fig. 13.—Endometrial sarcoma of malignant type, with many hyperchromatic nuclei and numerous mitoses. Patient aged fifty-three years.

In our own series of 59 cases, it was considered that in 39, or 66.1 per cent, the sarcoma was secondary in myomas. This gives an incidence of 0.56 per cent of sarcomatous degeneration in the 6,981 myomas com-

prised in our material, a figure somewhat lower than the 1.2 per cent of Kelly and Cullen in an earlier study from the same laboratory. It is also somewhat lower than the average reported in the recent literature. Klaften, for example, finds an incidence of 2.8 per cent; Kimbrough, 1.02 per cent; Frankl, 2.02 per cent; Steinhardt, 2.78 per cent; Franz, 0.64 per cent; Brings, 1.94 per cent; and Haase, 4.2 per cent. However, in 72,116 cases of myoma collected from the literature, Vogt found an incidence of only 0.41 per cent of sarcoma.

TREATMENT

Because of the difficulties of diagnosis, the treatment of sarcoma is often a matter of expediency rather than of deliberate planning. Only a few points of special interest need be touched upon here. The methods of treatment used in our own cases are put down simply as a matter of record, with the explanation that some at least were treated before the development of modern radio-therapy, so often a useful present-day adjunct.

TABLE VI

OPERATION	NUMBER OF PATIENTS	DEATHS WITHIN FIVE YEARS	
		NUMBER OF PATIENTS	PER CENT
Subtotal hysterectomy	29	8	36.4
Total hysterectomy	9	5	22.7
Vaginal myomectomy	4	2	9.1
Dilatation and curettage	4	1	4.5
Biopsy (including exploratory laparotomy)	4	3	13.6
Abdominal myomectomy	3	1	4.5
Removal of cervical polypus	2	–	–
Vaginal hysterectomy	1	1	4.5
Excision of cervix	1	1	4.5

X-ray therapy was employed in 12 cases and radium was applied to the uterus in 10 patients in addition to the operative procedure.

Surgery has been, and still is, the backbone of treatment, especially as so large a proportion of sarcomas are not discovered until operation for supposed myoma, or until the laboratory examination of such supposedly benign tumors. The possibility of sarcomatous change in myomas must always be borne in mind by the surgeon, and it is a wise precaution to cut into the tumor masses as soon as the uterus is removed, for a presumptive diagnosis of sarcoma can often be made from the gross appearance of the cut surface. When there is doubt on this point, frozen sections will often enable the decision to be made. If sarcoma is found or suspected, and especially when the lesion encroaches on the cervix, total hysterectomy is far safer than the supravaginal technique.

An experience which every surgeon of large experience must occasionally have is to receive a pathologic report of sarcoma after supravaginal hysterectomy for presumably benign myoma, and in some of these

at least the location of the lesion may make him doubtful as to whether to remove the cervix by a second operation or to depend upon postoperative radiation. With rare exceptions the latter course will probably be the wiser. Indeed, simple supravaginal hysterectomy, without radiation, has cured many cases of undoubted sarcoma. In our own series, many cases have been of this type, the patients' salvation lying in the fact that so many of the sarcomas developing in myomas are in a comparatively early stage and of a relatively low degree of malignancy. The same statement may possibly be made of radiotherapy, though we have no direct evidence on this point. Nothing is more certain than that an inevitable though small proportion of the many fibroids which have been treated by radiotherapy have been complicated by sarcoma, and yet sarcomatous recurrence after such treatment is practically unheard of.

On the other hand, even the most extensive surgery and the most complete radiotherapy will fail to cure the more malignant types of sarcoma when these have reached an advanced stage, as they unfortunately often do, before the patient comes to operation. These advanced cases are poor operative risks as a result of such factors as extreme anemia, cachexia and sepsis. This is indicated by the results shown in Kimbrough's series as well as our own. Palliation is often preferable to operations of the magnitude so often necessary in such advanced cases, assuming that the pathologic diagnosis has been made. In the less advanced and less malignant cases, on the other hand, the preferable plan of treatment is panhysterectomy followed by deep roentgenization.

END-RESULTS

In 50 of our cases it has been possible to secure information as to the postoperative histories. There were 14 patients alive and apparently well for varying periods up to three years following operation. This group, which includes a considerable number of the cases coming from outside sources, was either not traceable beyond three years or, in a few cases, too short a period had elapsed since operation. On the other

TABLE VII. SURVIVAL PERIOD IN FATAL CASES

SURVIVAL PERIOD	NUMBER OF PATIENTS IN 24 CASES
Death following operation:	
Within 14 days	7
5 weeks	1
7 weeks	1
7 months	3
9 months	4
11 months	1
3 years	1
4 years 10 months	1
7 years 2 months	1
10 years	2
Dismissed inoperable, death imminent	2

hand, 15 patients were alive and apparently well five years after operation, representing a five-year salvage of 30 per cent. It should be added, however, that 3 additional deaths occurred within ten years, reducing the ten-year cures to 12, or 24 per cent.

In addition to the 2 cases of sarcoma botryoides, which are always fatal, details as to the survival period were available in the 24 known deaths in this series.

SUMMARY

This study is based upon 59 cases of uterine sarcoma observed in our laboratory during a twenty-five year period, in a total material during that time of 26,972 case specimens, an incidence of 0.22 per cent. The highest age incidence was noted in the fifth decade of life. The symptomatology is not distinctive, and the diagnosis often difficult or impossible until operation and laboratory examination.

Sarcoma may arise from any of the constituent elements of the uterine wall or of uterine myoma, but is commonly of myogenic origin. It is probable, however, that it cannot arise, as was formerly believed, from mature muscle fibers, in spite of the apparent histologic transitions often seen. As with sarcoma elsewhere, its origin is almost certainly from unripe or undifferentiated muscle cell elements. The most common seat of origin is in myomas, the incidence of such change in our series being 0.56 per cent, though most authors have found it to be somewhat greater (1 to 1.5 per cent representing a fair estimate). The difficulties of determining the seat of origin (uterine wall, myoma, or mucous membrane) are discussed in the paper, as are the difficulties of classification. The most serviceable grouping is along general pathologic lines, into round, spindle, mixed, and perhaps, giant cell types.

The degree of mitotic activity is a good index of the degree of clinical malignancy of these tumors, as shown in the study of our own cases. The gross characteristics of uterine sarcoma permit of presumptive diagnosis in at least a proportion of cases. The treatment is often a matter of expediency rather than deliberate planning, especially as the disease is so often recognized only at or after operation. Surgery is therefore the backbone of treatment, with radiotherapy as a valuable adjunct.

While uterine sarcoma is a serious disease, the outlook is relatively good in the group arising in myomas. The mural and endometrial varieties are more unfavorable.

In our own series, a follow-up study was possible in 50 cases. Of these only 15 (30 per cent) were known to be living at the end of five years, and only 12 (24 per cent) at the end of ten years.

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DISCUSSION

DR. WILLIAM P. HEALY, New York, N. Y.—This Society has had two papers presented on this subject in a short space of time, one by Dr. Kimbrough three years ago, and Dr. Novak's today. Thus we have practically 200 cases from two outstanding institutions, and we may assume that the conclusions of these two papers bring the subject up to date for us.

As to the occurrence of this disease, Vogt, in a series of 72,000-odd cases collected from the literature, found that the incidence of sarcoma in association with myoma was about 0.46 per cent. At the Roosevelt Hospital, where I inquired several days ago, there have been within the last seven years four cases in about 1,200 cases of fibromyoma, or less than half of 1 per cent.

Now as to the prognostic importance of the recognized lesion, there are two general types, clinically and histologically, of sarcoma of the uterus: (1) The rather rare form develops from some portion of the uterus itself, and will be found to be extremely malignant, to contain many mitotic figures, and will be pleomorphic. (2) There are the sarcomas that occur in a previously existing myoma, of much less malignant quality, and these are the cases that I believe give the cures.

It is extraordinary that in these two series, aggregating approximately 200 cases, there have been obtained from 30 to 32 per cent of five-year cures. Dr. Kimbrough's series showed about 34 per cent and Dr. Novak's about 30 per cent. We have no such experience at the Memorial Hospital. Our cases are recognized first elsewhere and referred to, either as recurrent or as untreated. We could find only 23 cases in going through all of our material, and we have but 2 patients alive today. Each of these is a recent case, and each has pulmonary metastases. Hence, we feel the prognosis in sarcoma of the uterus is extremely bad.

We have one very interesting case of a patient under treatment. This patient, a woman less than forty-five years old, developed bloody sputum and a cough twelve months ago. By July, 1936, the diagnosis of a pulmonary tumor had been made through the Board of Health, to which she had been sent for diagnosis of tuberculosis. She was transferred to a cancer institution in the city which confirmed the diagnosis of a pulmonary tumor and discharged the patient as incurable. She finally arrived at the Memorial Hospital in October. A complete physical examination did not show any other lesion except a somewhat enlarged uterus. The patient had, however, had menorrhagia for the previous five months, and by January of this

year it had become metrorrhagia. She was then referred to my department, the uterus being then the size of a three and one-half months' pregnancy. The diagnostic curettage showed the so-called fish flesh material which is so diagnostic of sarcoma.

This patient had had her metastatic tumor identified before the primary. I want to emphasize that a woman at any age who has a tumor in her chest should be examined for the possibility of a primary tumor in the uterus, and when a sarcoma is found in the uterus it should also be looked for in the lung.

As to treatment with radiation, we have not cured a single case of sarcoma of the uterus with radiation.

DR. CAREY CULBERTSON, CHICAGO, ILL.—In the last two years I have had two cases of sarcoma of the uterus. The first one was a sarcoma botryoides combined with an adenocarcinoma in the fundus. The second case, an obese Bohemian woman, was operated upon with a provisional diagnosis of uterine fibroma. On opening the tumor after its removal it was seen that the growth was diffuse, not encapsulated. The surgical pathologist made a diagnosis of sarcoma of the so-called degenerative fibroid type.

That brings up the question as to whether these tumors are sarcomatous originally, or whether they are fibroids that have become sarcomatous, a theory I do not hold to strongly. This patient had no symptoms, had passed her menopause, had no leucorrhea, no bleeding, no pain and had not lost weight.

These two cases illustrate the differences that both Dr. Novak and Dr. Healy have referred to. We expect the second patient to get well. The first patient died within about fifteen months with metastases.

DR. KARL M. WILSON, ROCHESTER, N. Y.—Dr. Novak referred to a patient from whom I sent him a specimen for diagnosis. The patient was entirely unsuitable for surgery and she was treated only by radiation therapy. She got along very well for a year with no symptoms but now is on a rapid down hill course.

One other patient I have seen during the past year, was interesting because one-half of a myoma was solid calcification, the other was rapidly growing sarcoma. This patient also went rapidly down hill after her operation.

DR. NOVAK (closing).—As regards the incidence of sarcomatous degeneration of myomas, there would seem to be no doubt that the wide discrepancies to be found on this point are explainable by individual differences in the histologic criteria of sarcoma. The common error, especially in the earlier literature, was to mistake very cellular but perfectly benign myoma for sarcoma. Even now there is a residuum of cases in which pathologists will disagree, just as they do in the diagnosis of early carcinoma, because of similar differences of opinion as to criteria. Generally speaking, even a very cellular tumor should not be called sarcoma if the constituent cells exhibit striking uniformity and a complete absence of anaplastic activity. When, on the other hand, there is marked disparity of both nuclei and cytoplasm, with hyperchromatosis, possibly giant cells, and often mitoses, no other histologic diagnosis seems possible. The finding of mitoses in the individual section is not essential for diagnosis, but as a rule they are present, and we believe their number gives at least an approximate idea of the degree of malignancy of the tumor.

One of the sections I threw on the screen showed an unusually rich distribution of mitotic figures. It came from a private patient of my own who came under observation after almost exsanguinating bleeding. A diagnostic curettage done after transfusion established the diagnosis of sarcoma. Under radiotherapy and further transfusion her general condition improved so strikingly that a radical operation was carried out with excellent immediate result, but with rapid recurrence, metastases and death six or seven months later. In one of our patients metastasis occurred to the heart muscle and a similar case, in which I had the opportunity of studying sections, has been reported by Dr. Criscitiello, of Pittsfield.

THE CLINICAL SIGNIFICANCE OF ENDOMETRIAL HYPERPLASIA*

FRANKLIN L. PAYNE, M.D., PHILADELPHIA, PA.

AMONG the many points to be considered in appraising the clinical importance of endometrial hyperplasia are its rôle in benign uterine hemorrhage, whether it be functional or that associated with pelvic lesions, its relation to uterine myomas and endometriosis, its occurrence after the menopause, either with or without demonstrable pelvic pathology, and the part it plays in the development of fundal malignancy. The material for this study consists of 534 specimens of hyperplasia which were collected from 2,070 endometrial sections in the Laboratory of Obstetrics and Gynecology of the Hospital of the University of Pennsylvania. The specimens are divided into two groups, the premenopausal comprising 496 sections and the postmenopausal of 38.

PREMENOPAUSAL HYPERPLASIA

Endometrial hyerplasia may accompany every type of pelvic condition, with the exception of pregnancy and its complications (Table I).

TABLE I. PREMENOPAUSAL HYPERPLASIA, DISTRIBUTION OF 496 SPECIMENS

Functional bleeding	242 (48.8 per cent)
Myoma uteri	146 (29.5 per cent)
Myoma and endometriosis	8 (1.6 per cent)
Myoma and ovarian cyst	10 (2.0 per cent)
Myoma and pelvic inflammatory disease	11 (2.2 per cent)
Endometriosis	6 (1.2 per cent)
Ovarian cyst	13 (2.6 per cent)
Pelvic inflammatory disease	11 (2.2 per cent)
Pelvic floor relaxation	36 (7.3 per cent)
Hyperplasia and fundal carcinoma	8 (1.6 per cent)
Hyperplasia and cervical carcinoma	1 (0.2 per cent)
Functional dysmenorrhea	2 (0.4 per cent)
Functional amenorrhea	2 (0.4 per cent)

It is found in both functional uterine bleeding and functional amenorrhea, which suggests that it is not an important factor in either of these conditions. Approximately half of the specimens of premenopausal hyperplasia were obtained from patients with functional bleeding. The low incidence of functional amenorrhea with hyperplasia as shown in this study is a false estimate of its occurrence, because we have examined the endometria in so few cases of amenorrhea. However, in the light of our present knowledge that amenorrhea is not always due to quantitative ovarian deficiency, we believe that the performance of

*Read, by invitation, at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

endometrial biopsies in this condition will disclose many more instances of its association with hyperplasia.

Next to functional bleeding the greatest number of hyperplasias occurred in combination with uncomplicated uterine fibroids, 29.5 per cent of the total. The third highest number of hyperplasias appeared in association with relaxation of the pelvic floor, which accounted for 36 (7.3 per cent) of the total number. Most of these patients had experienced no menstrual abnormalities, but were subjected to diagnostic curettage prior to plastic procedures. Eight (1.6 per cent) of the hyperplasias were associated with fundal malignancy and one with cervical carcinoma. The wide distribution of hyperplasia herein shown arouses the suspicion that it is a coincidental occurrence rather than a symptom-producing entity.

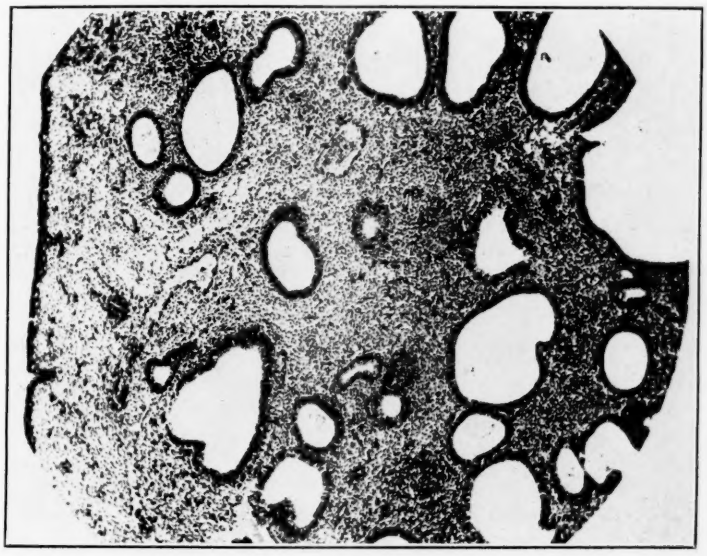

Fig. 1.—(Gyn. Path. No. 10,909. ×90.) Typical hyperplasia. Patient aged fourteen years. Continuous bleeding from onset of menstruation, at eleven years, until this curettage.

The frequent association of hyperplasia with functional bleeding has led to the belief that one is a necessary adjunct to the other. A typical example of this association is seen in Fig. 1. This specimen was obtained from a child of fourteen years whose menstruation began at eleven and continued without interruption until the curettage was done. All of the characteristic features of hyperplasia are seen in this section. A similar picture is shown in Fig. 2 from a patient twenty-four years of age with oligomenorrhea who, after a year's amenorrhea, had spotted at irregular intervals for nine months, but had experienced no bleeding for the last four months. Four other biopsy specimens were collected at weekly intervals and all showed hyperplasia. Simultaneous

blood and urine studies revealed evidence of persistent hyperestrinism throughout the five weeks of observation.

Evidence that hyperplasia and long periods of amenorrhea are compatible is seen in Fig. 3, from a patient thirty-four years of age who had not menstruated for eight years. A week following the curettage,

Fig. 2.—(Gyn. Path. No. 18,008. ×154.) Hyperplasia with oligomenorrhea. Patient aged twenty-four years. Irregular scanty periods for two years. Last period four months ago.

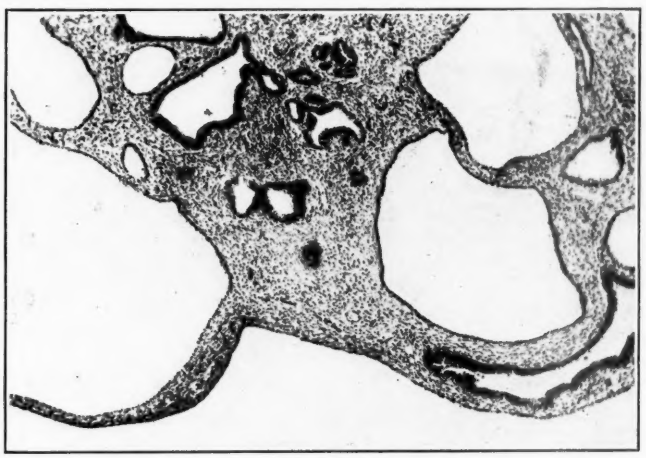

Fig. 3.—(Gyn. Path. No. 16,328. ×115.) Hyperplasia with amenorrhea. Patient aged thirty-four years. No period for eight years.

profuse uterine bleeding occurred. While amenorrhea with hyperplasia probably is a common occurrence, determination of its actual incidence must await a large series of endometrial biopsies.

On the other hand, abundant information is available concerning the incidence of hyperplasia in functional bleeding, uterine myomas, endometriosis and various adnexal lesions, as is shown in Table II. In this

TABLE II. PREMENOPAUSAL HYPERPLASIA, INCIDENCE IN ITS COMMONLY ASSOCIATED CONDITIONS

	NUMBER OF ENDOMET. SPECIMENS	PERCENTAGE OF HYPERPLASIA
Functional bleeding	676	35.8
Myoma uteri	750	19.4
Myoma and endometriosis	84	9.5
Myoma and ovarian cyst	31	32.2
Myoma and pelvic inflammatory disease	152	7.2
Endometriosis	55	10.9
Pelvic inflammatory disease	101	10.9
Ovarian cyst	30	43.3

Total number of endometrial specimens, 1,879
Total number of hyperplasias, 447 (24.0 per cent)

series, the endometrial sections from 676 patients with functional bleeding showed hyperplasia in 35.8 per cent. These figures confirm the opinion of both myself and others that endometrial hyperplasia is not a necessary, nor even an usual, accompaniment to abnormal bleeding of functional origin.

The frequent association between hyperplasia and uterine myomas has been emphasized by numerous authors, who found the following incidence: Witherspoon, 40 hyperplasias in 44 myomas; King, 71 per cent in 114 cases; Kanter and Klawans, 53 per cent in 100 uteri; and E. M. Blair, 80 per cent in 83 specimens. The incidence of hyperplasia in our series did not approach these figures. Of 750 uncomplicated myomas, hyperplasia was found in 146 (19.4 per cent). By adding to these the tumors complicated by adnexal lesions a total of 1,017 is obtained, 17 per cent of which had associated hyperplasia. Such a low incidence of hyperplasia in association with myomas does not indicate a common etiology for the two conditions.

Witherspoon suggests that endometriosis and endometrial hyperplasia may result from a common stimulus. The occurrence of 10.9 per cent of hyperplasia in 55 cases of endometriosis in the present series does not support his theory.

Except for functional bleeding, the highest incidence of hyperplasia accompanied ovarian cysts (43.3 per cent). By including the uncomplicated cysts with those associated with myomas, 23 specimens were available. Five of these were neoplastic and 18 were retention cysts of the follicular type. The common association of hyperplasia and follicular cysts of the ovary is generally recognized. On the other hand, hyperplasia may occur with normal ovaries containing active corpora lutea, as was pointed out by Novak and Martzloff. Recently, we found hyperplasia along with a typical corpus luteum cyst. This occurrence casts doubt upon the commonly accepted opinion that hyperplasia always results from unbridled follicular stimulation in the absence of the luteal hormone. Possible direct influence by the anterior lobe secretion

has been suggested, and Hoffbauer has reported overgrowth of the basal endometrial layer in castrate animals following injections of anterior lobe extracts. The microscopic similarity between hyperplasia and the active basal layer lends support to the possibility that both are controlled by the same hormonal influence, which may arise in the hypophysis. Acceptance of this theory would explain postmenopausal hyperplasia.

The dual occurrence of hyperplasia and abnormal uterine bleeding has been recognized since this endometrial change was first described. Witherspoon states that "endometrial hyperplasia is characterized by profuse and irregular bleeding from the uterus." Fluhmann found the outstanding symptom of hyperplasia to be abnormal uterine bleeding. Graves emphasized the almost universal presence of gland dysplasia in arrhythmic dysfunctional bleeding. The opposite opinion is voiced by Kurzrok and Wilson, who state that "functional bleeding is completely independent of the type of endometrium." The present study indicates that abnormal bleeding is not a necessary accompaniment to endometrial hyperplasia, and that hyperplasia is not an essential adjunct to dysfunctional bleeding.

Discussion of the types of bleeding in this paper includes the term "abnormal" to mean menorrhagia, metrorrhagia, menometrorrhagia, or polymenorrhea. The term "normal" designates bleeding at regular intervals, of the average duration and amount with no recent change in its characteristics. We realize that such bleeding from a hyperplastic endometrium is not normal menstruation in the strict physiologic sense. "Oligomenorrhea" in this discussion denotes scanty periods, either as to interval, amount or duration, including all instances of temporary cessation of periods up to four months. After that time the term "amenorrhea" is applied.

The clinical records of 487 patients with endometrial hyperplasia show that abnormal bleeding occurred in 85.2 per cent and normal, scanty, or absent periods in 14.8 per cent (Table III). Of the latter

TABLE III. PREMENOPAUSAL HYPERPLASIA, RELATIONSHIP OF AGE TO ABNORMAL BLEEDING

(Exclusive of Nine Cases Associated With Uterine Malignancy)

AGE	NUMBER	ABNORMAL PER CENT	NORMAL PER CENT	OLIGOMENORRHEA PER CENT	AMENORRHEA PER CENT
10-19	14	100.0	0.0	0.0	0.0
20-29	42	80.0	17.0	0.0	3.0
30-39	121	79.0	16.5	3.6	0.9
40-49	253	86.5	11.1	1.9	0.5
50-59	57	94.5	1.7	1.8	1.8
Total number	487				
Abnormal bleeding				415 (85.2%)	
Normal, scanty or absent periods				72 (14.8%)	

group of 72 patients, 56 had normal periods, 10 had oligomenorrhea, and 6 were amenorrheic for intervals of four months to eight years. Two cases of amenorrhea were functional, and one occurred with each of the following conditions: Pelvic inflammatory disease, uterine descensus, paraovarian cyst and myoma uteri. This list is fairly representative of the conditions in which hyperplasia and abnormal bleeding are usually found, yet these amenorrheic patients lacked something to stimulate, or possessed something to prohibit, uterine bleeding.

So far as age is concerned, the incidence of abnormal periods is seen to be about equal from the third to the fifth decade of life, with a sharp increase after this age suggesting the occurrence of some hormonal change after forty years of age which increases the tendency to bleed. In this series, the high incidence of flooding with hyperplasia in the second decade is expected for, with rare exceptions, abnormal bleeding

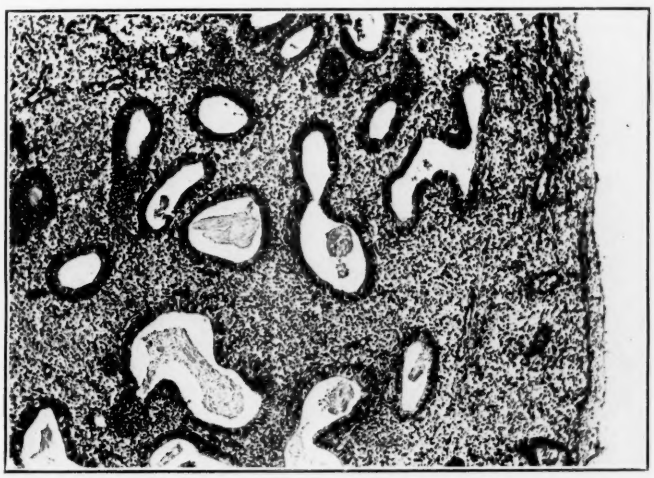

Fig. 4.—(Gyn. Path. No. 10,821. ×130.) Hyperplasia with regular periods. Patient aged forty-four years. Last period ceased eight days before this curettage.

was the only indication for curettage. From the third to the fifth decade, normal periods frequently accompany endometrial hyperplasia. An example of this is seen in Fig. 4 which shows the endometrium of a patient, forty-four years old, upon whom a repair was performed. Her menstrual periods had always been normal, the last having ceased eight days before the curettage. The normal proliferative phase has been replaced by typical endometrial hyperplasia.

Further evidence of the diversity between the incidence of hyperplasia and of abnormal bleeding is seen in Table IV. A marked variation in the frequency of menstrual irregularities occurred, despite the presence of endometrial hyperplacia in all of the specimens. The most striking difference is the 89 per cent incidence of irregular bleeding in myoma with hyperplasia against 45 per cent in pelvic inflammatory disease. Abnormal bleeding was present in 70 per cent of the uncom-

plicated ovarian cysts with hyperplasia. By combining these with the cysts complicated by myomas to make a total of 23, a 61 per cent incidence of menstrual aberrations is noted (Table V). Eighteen of the

TABLE IV. PREMENOPAUSAL HYPERPLASIA, INCIDENCE OF ABNORMAL BLEEDING IN ITS ASSOCIATED CONDITIONS—447 CASES

	ABNORMAL PER CENT
Functional bleeding	100
Myoma uteri	89
Myoma and endometriosis	50
Myoma and ovarian cyst	50
Myoma and pelvic inflammatory disease	82
Endometriosis	83
Pelvic inflammatory disease	45
Ovarian cyst	70

TABLE V. PREMENOPAUSAL HYPERPLASIA, RELATION OF ASSOCIATED OVARIAN CYSTS TO THE CHARACTER OF BLEEDING—TOTAL NUMBER, 23

Retention cysts	18	Abnormal bleeding	13 (72 per cent)
Neoplastic cysts	5	Abnormal bleeding	1 (20 per cent)
Total with abnormal bleeding 14 (61 per cent)			

23 were retention cysts and excessive bleeding accompanied 13 (75 per cent). Of the five neoplastic cysts, menstrual disturbances occurred in only one (20 per cent). These figures suggest the possibility of a mutual background for the development of the retention cysts of the ovary and for the occurrence of irregular uterine bleeding.

POSTMENOPAUSAL HYPERPLASIA

Postmenopausal hyperplasia is found both in the presence and in the absence of demonstrable pelvic pathology. Frequently it is not accompanied by uterine bleeding. In this study, no patient was considered to be postmenopausal unless she had reached the menopausal age and had gone a year without uterine bleeding. There were 38 such patients, ranging from one to twenty-three years after the menopause.

That postmenopausal hyperplasia occurs in a wide variety of pelvic conditions is shown in Table VI. Unlike premenopausal hyperplasia, a

TABLE VI. POSTMENOPAUSAL HYPERPLASIA, DISTRIBUTION OF 38 SPECIMENS

Ovarian carcinoma	4 (11 per cent)
Granulosa cell carcinoma	2 (5 per cent)
Fundal carcinoma	4 (11 per cent)
Cervical carcinoma	1 (2 per cent)
Pelvic floor relaxation	3 (8 per cent)
Ovarian cyst—benign	3 (8 per cent)
Myoma uteri	8 (21 per cent)
Unexplained uterine bleeding	13 (34 per cent)

high incidence of associated malignancy is noted, 11 (29 per cent) of the 38 cases in this group. Of the begign lesions, the most frequent to

be associated with postmenopausal hyperplasia was the myoma (21 per cent). No pelvic pathology, except the endometrial hyperplasia, was found in one-third of the patients, all of whom were curetted because of postmenopausal bleeding. Of the 13 patients in this group, the intervals between the menopause and the onset of symptoms were two to five years, 2 patients; five to ten years, 3 patients; ten to twenty years, 6 patients; twenty to twenty-three years, 2 patients.

The occurrence of hyperplasia at this age has not been explained satisfactorily.

Taylor suggested that it may be the remains of premenopausal hyperplasia, but it is difficult to comprehend why the endometrium should not accompany the other pelvic structures in their atrophic changes. Novak has made two suggestions, pos-

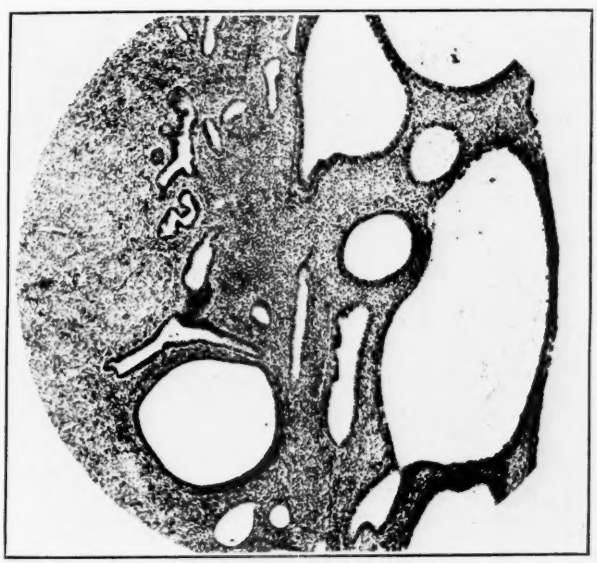

Fig. 5.—(Gyn. Path. No. 17,753. ×74.) Postmenopausal hyperplasia. Patient aged fifty-five years. Menopause at forty-nine years. No bleeding since.

sible postmenopausal continuance of estrin production by the ovaries and the possibility that the anterior pituitary lobe may assume estrogenic function after the menopause. The latter theory is supported by the report by Frank and Goldberger of the urinary excretion of the estrogenic factor by 12 surgical castrates. Hoffbauer's stimulation of the basal endometrium in castrates with anterior pituitary extracts suggests that postmenopausal hyperplasia may arise from anterior lobe stimulation.

While this problem is still in the realm of conjecture, it is no more uncertain than the explanation of postmenopausal uterine bleeding in the absence of accountable pelvic pathology. Evidence that hyperplasia *per se* does not cause the bleeding is seen in the fact that 11 of the 33 patients with postmenopausal hyperplasia had not bled since the menopause (Table VII). The conditions which obviously cause bleeding, cervical and fundal malignancy, are excluded from this table. Fig. 5

shows typical hyperplasia from a patient who was operated upon six years after her menopause for a pseudomucinous cyst of the ovary.

Fig. 6.—(Gyn. Path. No. 13,154. ×90.) Postmenopausal hyperplasia with bleeding. Patient aged sixty years. Menopause at forty-nine years. Bleeding for eight days, as free as a period.

Fig. 7.—(Gyn. Path. No. 19,393. ×90.) Postmenopausal hyperplasia with bleeding. Patient aged sixty-six years. Menopause at fifty-nine years. Scant irregular bleeding for a month.

There had been no bleeding since the menopause. Just why that patient should not bleed, and both of the patients of the following specimens should do so, cannot be explained.

Fig. 6 was obtained from a patient whose bleeding occurred eleven years postmenopausally. At the time of the curettage, the endometrial tissue was benign. She was given 600 mg. hr. of intrauterine radium, with no recurrence of symptoms. Fig. 7 was recovered seven years after the menopause. The curettings were benign and 1,200 mg. hr. of radium were administered with no subsequent bleeding.

TABLE VII. POSTMENOPAUSAL HYPERPLASIA, INCIDENCE OF BLEEDING—33 PATIENTS

(Cases of Associated Uterine Malignancy Excluded)

	BLEEDING	NO BLEEDING
Myoma uteri	6	2
Ovarian cyst, benign	0	3
Ovarian carcinoma	1	3
Granulosa cell carcinoma	1	1
Pelvic floor relaxation	1	2
Unexplained bleeding	13	0
	22 (66.6 per cent)	11 (33.3 per cent)

TABLE VIII. POSTMENOPAUSAL HYPERPLASIA, TREATMENT

Hysterectomy and bilateral salpingo-oophorectomy	20
Dilatation and curettage	5
Dilatation and curettage and intrauterine radium, 600 mg. hr.	3
Dilatation and curettage and intrauterine radium, 1,200 mg. hr.	5
Dilatation and curettage and intrauterine radium, 2,400 mg. hr.	4
Dilatation and curettage and intrauterine radium, 3,600 mg. hr.	1

Table VIII shows the treatment of the 38 patients with postmenopausal hyperplasia. Of the 18 who were not treated by hysterectomy, 4 had myomas, 2 relaxation of the pelvic floor, and 12 unexplained uterine bleeding. A simple curettage was done for 5 and for the remainder, curettage and intrauterine radium of the dosage indicated. Those who received 2,400 to 3,600 mg. hr. of radium had curettings which were so suggestive of malignancy that it was only after careful microscopic study that this diagnosis was disproved. The remainder were apparently benign at the time of the curettage, and microscopic study verified this opinion. Of the 18 patients, 4 were treated from one to two years ago, 5 from four to six years ago, and 9 from six to twelve years ago. Seventeen had no recurrence of symptoms and one reported the return of spotting six years after a curettage and 1,200 mg. hr. of radium. A second curettage revealed nothing malignant and four years have elapsed with no further symptoms. That the hyperplasia occurred in this group of patients without associated ovarian neoplasm is proved by the facts that no adnexal pathology was demonstrable at the original examination and that the bleeding has not recurred up to the present time. The absence of bleeding for intervals ranging from one to twelve years also warrants the assumption that in no instance has malignancy been engrafted upon the hyperplasia.

HYPERPLASIA AND FUNDAL CARCINOMA

The relationship between endometrial hyperplasia and fundal carcinoma has been the subject of considerable discussion. We have not started with the fundal malignancies and searched for hyperplasia, as Novak did, but we have searched for malignancy in the specimens of hyperplasia, with the following results. Of 2,070 endometrial specimens, hyperplasia was found in 534 (25.8 per cent). Thirteen (2.4 per cent) of the hyperplasias were associated with fundal carcinoma (Table IX). If hyperplasia predisposes to carcinoma the incidence of malignancy should exceed the 2.4 per cent herein recorded.

By dividing the specimens into pre- and postmenopausal groups we found associated malignancy in 1.8 per cent of the first, and 10.5 per cent of the latter, showing the frequency of postmenopausal hyperplasia

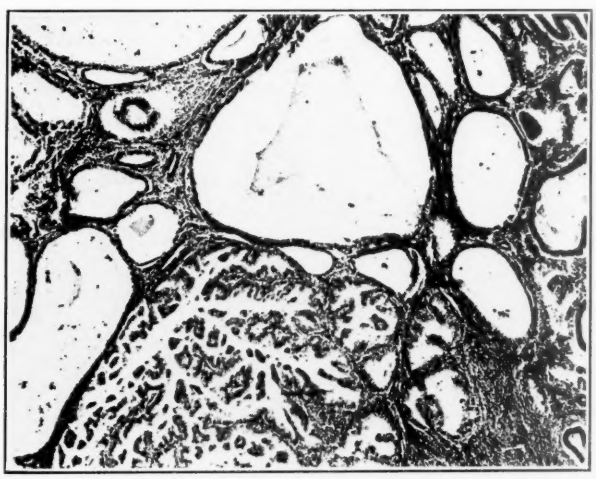

Fig. 8.—(Gyn. Path. No. 16,079. ×90.) Postmenopausal hyperplasia with superimposed adenocarcinoma.

TABLE IX. ENDOMETRIAL HYPERPLASIA, INCIDENCE OF FUNDAL CARCINOMA

Number of endometrial specimens		2,070
Number with hyperplasia		534 (25.8%)
Superimposed carcinoma		13 (2.4%)
Premenopausal hyperplasia	496	
Superimposed carcinoma	9	(1.8%)
Postmenopausal hyperplasia	38	
Superimposed carcinoma	4	(10.5%)

with carcinoma to be 5.8 times that of the premenopause. This figure is less significant when we are reminded that the usual incidence of postmenopausal fundal malignancy is 3 to 4 times that of the premenopausal era. Two hundred forty-one specimens of fundal malignancy in our laboratory are divided into premenopausal 54 and postmenopausal 187, the latter being 3.3 times as frequent as the former.

While malignancy occasionally accompanies hyperplasia, the clinical importance of this association depends less upon the predisposition of hyperplasia to the development of carcinoma, than upon the possibility that an obscure area of malignancy may be overlooked, or may not be sectioned, in an endometrial specimen which is dominated by hyper-

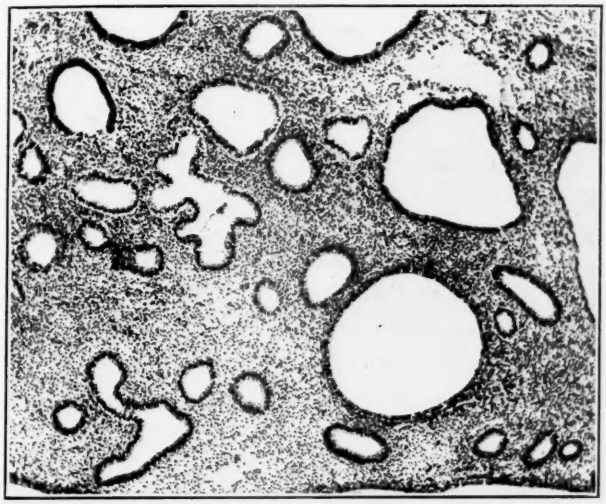

Fig. 9*A*.—(Gyn. Path. No. 16,598 × 95.) Typical hyperplasia. Patient aged forty-eight years. Irregular bleeding for three months, after eight months amenorrhea.

Fig. 9*B*.—(Gyn. Path. No. 16,598. ×135.) Hyperplasia with superimposed carcinoma.

plastic changes. Such an error would seem impossible in the light of Fig. 8, showing postmenopausal hyperplasia in juxtaposition to obvious carcinoma. Fig. 9, however, depicts a different situation and demonstrates the value of multiple sections from endometrial curettings. First (Fig. 9*A*), is the typical hyperplasia recovered from a patient forty-eight years old, with irregular bleeding for three months, following eight

months of amenorrhea. In another slide (Fig. 9*B*), cut from the same block, the area of carcinoma was found. That this occurrence is not limited to older patients is evidenced by the fact that 3 of the 9 patients with premenopausal hyperplasia with carcinoma were less than forty years of age. Gross examination of the curettings may be misleading, for it enabled the diagnosis of malignancy in only 5 of the group. In the other 4 the characteristic macroscopic appearance of hyperplasia prevailed, and it was only upon microscopic study that the carcinoma was detected.

SUMMARY AND CONCLUSIONS

The clinical records of 534 patients with endometrial hyperplasia have been analyzed in the effort to determine its rôle in benign uterine hemorrhage, both before and after the menopause, and to evaluate the significance of its association with myomas, endometriosis and fundal carcinoma.

The presence of hyperplasia usually implies abnormal bleeding, but this is not a constant occurrence for such bleeding accompanied only 85 per cent of the premenopausal hyperplasias in this study. The remainder were attended by normal periods, oligomenorrhea or amenorrhea. When hyperplasia was found to be associated with other pelvic lesions, the frequency of abnormal bleeding varied according to the type of complicating lesion. Of the myomas with hyperplasia, 89 per cent had irregular periods, against 70 per cent of the ovarian cysts and 45 per cent of the cases of pelvic inflammatory disease. Such variation, despite the constant presence of hyperplasia, suggests that some influence other than the endometrial change precipitated the pathologic bleeding. Further evidence that hyperplasia does not necessitate abnormal bleeding is noted in the fact that one-third of the patients with postmenopausal hyperplasia had experienced no bleeding since the menopause. Just as hyperplasia may occur without abnormal bleeding, so may abnormal bleeding occur without hyperplasia. Approximately two-thirds of the cases of functional uterine hemorrhage in the present series yielded endometria which were devoid of hyperplasia.

The significance of the association between hyperplasia and benign pelvic lesions, as myomas, endometriosis, pelvic inflammatory disease and ovarian cysts, is uncertain. The theory that myomas and hyperplasia have a common etiologic basis loses support by the occurrence of hyperplasia in only 17 per cent of the myomatous uteri in this study. If the two conditions are allied in origin, the 496 specimens of hyperplasia should have been accompanied by myomas more frequently than one out of three times, as occurred in this series. The absence of myomas in 65 per cent of the hyperplasias and the absence of hyperplasia in 83 per cent of the myomas suggests different origins for the two conditions.

The incidence of hyperplasia in association with endometriosis was the same as that found in pelvic inflammatory disease (10.9 per cent), while 43 per cent of the ovarian cysts were accompanied by hyperplasia. We consider hyperplasia in these conditions to be the endometrial response to disturbed ovarian function and hope that the unusually high incidence of hyperplasia in ovarian cysts will be explained by hormone studies upon the cyst fluid, which we are now in the process of making.

The existence of certain points of similarity between the microscopic appearance of marked hyperplasia and of fundal malignancy is generally conceded. While the stimulative processes which produce hyperplasia theoretically might continue until the endometrium assumes malignant characteristics, the 2.4 per cent incidence of hyperplasia with superimposed carcinoma in this study indicates that, if this excessive stimulation does occur, it must do so with extreme rarity. It has been suggested postmenopausal hyperplasia particularly favors the development of carcinoma. Its occurrence in this series, 5 times more often than in the premenopause, would seem to support the suggestion, except that postmenopausal fundal carcinoma is generally conceded to be 3 to 4 times as common as premenopausal, regardless of the type of the associated endometrium. The significance of the association between hyperplasia and fundal malignancy seems to lie more in the danger that the hyperplasia may so dominate the pathologic picture as to obscure the malignant change than in the likelihood that it will favor the development of carcinoma.

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DISCUSSION

DR. KARL H. MARTZLOFF, Portland Ore.—Hyperplasia endometrii twelve to fifteen years ago was a term employed in only a few laboratories. Now, however, the pendulum has swung so far that one sees the term hyperplasia endometrii applied to virtually any interval type of endometrium associated with abnormal uterine bleeding. Certainly if this term is used its use should be restricted to the characteristic process to which it was first applied by Cullen and to which it has been restricted by Novak, Schroeder, TeLinde, Fluhmann, and others.

The occurrence of hyperplasia endometrii in the presence of amenorrhea, or more commonly with a history of amenorrhea preceding the bleeding phase, is also not generally appreciated and has been clearly reemphasized by Dr. Payne as occurring in 6 per cent of the University of Pennsylvania material. This phenomenon has

also been noted by Schroeder and was noted by Novak and Martzloff in 16.9 per cent of their material. However, I do not believe that in the case of the thirty-year-old patient, mentioned by Dr. Payne, who had not menstruated for eight years, that one should infer that this patient's endometrium was hyperplastic during this entire period, or that one may reasonably assume an apparently causative hyperestrinemia to have existed during the preceding eight-year interval.

Dr. Payne has observed also that in 56 (11.4 per cent) of his patients there was a history of normal menstruation in the presence of hyperplasia. In fact, 36 (7.3 per cent) of his specimens represented routine curettings obtained from patients about to undergo reparative operations on the birth canal. This corresponds closely to a similar group of patients, reported from Cullen's clinic, who also gave a history of normal menstruation. It is worth noting, however, that these figures, just as Dr. Payne's, are based on histories generally obtained by others from ward patients who, at times, are very unobservant of menstrual abnormality.

The question of the histologic criteria used by individual investigators in recognizing hyperplasia is of fundamental importance. If moderate variations in the size of endometrial glands are to be interpreted as abnormalities then one is plunged immediately into confusion. For, after all, the normal variation that occurs in gland shape, luminal diameter and tinctorial reaction in various fields and even in a single low power field of the zona compacta and spongiosum of a normal endometrium may be marked. This occurs whether the endometrium is a menstruating one, as shown so well by Bartelmez and Culbertson, or whether it is in the preovulatory or postovulatory phase of the intermenstruum.

This uneven response of similar layers of the endometrium to an apparently uniform hormonal stimulus, while probably not generally appreciated, nevertheless has been known for years. It probably indicates that the endometrium, as an end organ, so to speak, for the action of the ovarian hormones, must vary in its receptivity to a given hormonal stimulus.

Normal uterine glands during the various phases of the intermenstruum may vary from about 16 to 160 microns in their short diameters. A difference in the gland diameters of 30 to 80 microns in the same microscopic field of normal endometrium where the diameters ordinarily are less than 160 microns, is a common observation.

It would be helpful if one could reduce the most spectacular phase of hyperplasia endometrii to a mathematical formula, for difference in gland size along with large glands is one of its arresting and most easily recognized characteristics. In unmistakable preparations the differences between maximum and minimum diameters in a single field are generally greater than 150 microns. However, if the gland diameters in a given area are all over 250 microns, obviously variations are no longer diagnostically significant for the glands are all abnormally enlarged.

The section shown by Dr. Payne as an example of typical hyperplasia from a woman with a normal menstrual history impresses me more as that of a normally developing endometrium probably reflecting a late preovulatory or an early postovulatory or progestin response and showing also the picture of uneven development or so-called irregular ripening. If my surmise is correct that these endometria represent merely normal variations, it will help explain the large number of so-called hyperplastic endometriums obtained by Dr. Payne from women with normal menstrual histories.

The extremely dilated glands, measuring 800 to 1,000 microns in diameter which are lined by flattened epithelium and occur in some postmenopausal or occasional amenorrheic endometria, are I believe controversial. To accept them as unequivocal evidence of an active or preexisting hyperplasia is probably debatable, if other supportive evidences of hyperplasia such as large glands lined by columnar epithelium, mitoses, etc., are lacking.

Histologic study of these endometriums may be of some prognostic value in the premenopausal group. If, for example, the endometrium shows a bona fide widespread hyperplasia, the outlook for the correction of the underlying glandular dysfunction and the reestablishment of a normal menstrual cycle by conservative measures is, I believe, relatively poor. Contrariwise, if isolated and infrequent areas of hyperplasia occur in an endometrium that in most areas shows its apparent ability to respond normally to hormonal stimuli, then the outlook for recovery without resorting to radiation or hysterectomy is appreciably better.

DR. CAREY CULBERTSON, CHICAGO, ILL.—One thing is usually left out in discussions of the factors behind hyperplasia. That is the question of multiparity. Special consideration should be given the regeneration of the endometrium following labor or abortion. Regeneration is never 100 per cent perfect any more than involution is 100 per cent perfect in the uterine mucosa.

The first section shown in the slides is not a hyperplasia. It is what would be called a normal endometrium, but the woman has had 8 children. She is forty-four years of age and was bleeding excessively, hypermenorrhea of the menorrhagic type.

This section, which represents the general condition throughout the whole endometrium, resembles a benign adenoma, with little or no stroma. Now it is the stroma that is required for the production of decidua and the reception of a fertilized egg, and it seems to me to be of first importance in considering the significance of a given endometrial pattern.

This second slide shows the ordinary hyperplasia or irregularity of the glands. It is about two times as thick as the normal endometrium.

The third shows a hyperplasia in a young woman with an abundance of stroma. It is in the pregravid stage and resembles very much the decidua of pregnancy. One might easily mistake these glands for the "glands of pregnancy" that we are all familiar with.

In the next slide is shown the hyperplasia of the Swiss-cheese type. There are markedly dilated glands but still there is enough stroma left. This woman had borne only one child.

The fifth slide is from a woman forty-two years of age who had had 9 children and two abortions. Longitudinal and cross-section of this tissue shows an almost entire absence of stroma. This is, however, a hyperplasia, the endometrium being about three times as thick as normal.

All of this brings up problems relative to endometrial regeneration and the stimulus involved. It would appear that the epithelial elements regenerate better than the stroma, when this regeneration takes place repeatedly.

DR. EMIL NOVAK, BALTIMORE, MD.—Constant reference is made to the confusion in the microscopic diagnosis of hyperplasia, and this confusion unquestionably exists. The reason for this lies in the fact that at one time we all believed that the characteristic endometrial finding in cases of functional bleeding was that of typical hyperplasia, and the tendency has been to fit the microscopic diagnosis to the clinical diagnosis of functional bleeding.

We have long since in our own laboratory ceased to make such labored diagnoses, for it has become clear that functional bleeding may occur not only from an endometrium of the typical Swiss-cheese pattern, but also from one of the normal interval or secretory type, or even from an atrophic mucosa. The same statement can be made with reference to amenorrhea. Unless one invokes some unknown special bleeding factor, the evidence for which is rapidly dwindling, such observations point clearly to the fact that the "bleeding level" of the endometrium exhibits marked individual variations, and that the spill of blood may occur at different

hormone levels, just as the urinary spill of sugar may occur at different blood sugar levels. This viewpoint I have already presented in the discussion of Dr. Ross' paper.

The diagnosis of hyperplasia should, therefore, be reserved for the cases in which there is a greater or less degree of proliferation of the endometrial elements, though it is difficult to draw hard and fast rules as to where normal proliferation ends and where the abnormal begins. In the common type of functional bleeding the underlying cause is a failure of ovulation, with a persistence of estrone effect, and an absence of the corpus luteum hormone and its effects. In the much smaller group of functional bleeding cases in which a secretory endometrium is found, the mechanism is different, though the bleeding may be just as truly functional. Hyperplasia represents simply a maximum growth effect, and nothing seems more clearly established than that the growth effects of estrone do not necessarily parallel the bleeding propensities of the endometrium. The factor which seems far more important in bringing about the bleeding spill is the quantitative hormonal interreaction of the hypophysis and the ovaries.

I do not believe there is any worthwhile evidence to associate myoma and hyperplasia casually, especially in view of the fact that myoma occurs also in many other organs and tissues in which a hormonal relation is difficult to conceive of. There is much more reason, it seems to me, to associate hyperplasia, which is an endometrial overgrowth, with uterine adenomyosis, which is a similar endometrial overgrowth carried to the point of invasion of the musculature, plus a striking overgrowth of the latter.

I agree with Dr. Payne that no evidence exists to indicate that the common type of hyperplasia seen during reproductive life predisposes to adenocarcinoma, but I do believe that an important relation of some sort exists between postmenopausal hyperplasia and adenocarcinoma on the basis of evidence from our laboratory which I presented before this Society last year. I cannot review this here, but I may say that we have during the past year encountered quite a group of cases again illustrating this relationship, and are more than ever convinced of its possible importance.

DR. C. FREDERIC FLUHMANN, SAN FRANCISCO, CALIF.—Early studies of hyperplasia were based solely on the histologic picture of the endometrium and many speculations were made as to the etiology of the condition. More recent work has served to show that it is the manifestation of an endocrinologic disturbance, and it has been possible to reproduce it in both experimental animals and in castrate women. There can scarcely be any question that it is bound up with the action of estrogenic hormones which are either manufactured or possibly merely changed and utilized by the ovaries. These substances are known to be stimulants to endometrial growth, and under conditions as yet not too well understood, they may result in the intense overgrowth of the uterine mucosa which we know as hyperplasia. I can find no necessity for attributing this additional quality to the many virtues of the anterior hypophysis, especially since this concept is based on incomplete experimental work performed with another species and as yet unconfirmed.

It thus seems established that hyperplasia results from a stimulation by estrogenic hormones, in the absence of a corpus luteum influence—and not necessarily by a hyperestrinism but even by a prolonged constant stimulation of small amounts of the hormone. On the other hand, it is difficult at the present to explain the occurrence of bleeding in such cases. Uterine hemorrhage may occur as a persistent metrorrhagia, as a type of cyclic bleeding such as is found in the anovulatory cycles of monkeys, and this endometrial picture is often noted in patients with longer or shorter periods of amenorrhea. It is futile to speculate at present on the actual mechanism of the hemorrhage, and I fail to see how an explanation can be given be-

fore the factors concerned with bleeding in normal menstruation have been definitely determined. I should like to draw your attention again, however, to the increase in the estrogenic hormone content of the blood which is associated with the onset of bleeding in patients with hyperplasia. This represents a departure from the normal and may prove of considerable significance.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—We have over a period of fifteen years seen many uteri at or beyond the menopause which were of the subinvolution type, free from myomas, and from which we have obtained a gross amount of endometrial tissue which suggested the probability of cancer and in which in each instance we have placed radium within the uterine cavity in a dosage running from 1,000 to 1,400 millicurie hours. The pathologist has examined the tissue in all of the cases and often failed to find cancer. Instead he has reported hyperplastic glandular endometrium to our surprise. In no single instance has cancer to our knowledge subsequently developed, despite the large amount of endometrial tissue present and its intense hyperplastic structure. The rather small amount of initial uterine radiation, not exceeding 1,400 millicurie hours, has apparently permanently prevented the development of cancer in these cases.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—We have seen specimens of curettings in the laboratory where many sections show the "Swiss-cheese" type of gland, but in which if we block every bit of tissue we find a small area of carcinoma. Diagnosis from a frozen section of curettings is, I think, an extremely hazardous procedure.

Two years ago I was called to examine a frozen section of curettings removed from a patient upon whom an interposition operation was about to be done. I studied several slides and found nothing but benign hyperplasia. I reported this, stating the danger of such an examination, and asked that the operation be postponed until the next day when I could study more satisfactory slides of all the material. In spite of this, the interposition operation was done and the final section showed definite adenocarcinoma of the corpus. This clearly emphasizes the importance of studying all the material removed by the curette.

DR. FRANKLIN L. PAYNE (closing).—Dr. Fluhmann's statement that it is unnecessary to enlist the function of the anterior lobe to explain the development of hyperplasia is probably correct. The commonly accepted explanation of hyperestrinism, however, does not account for the presence of postmenopausal hyperplasia in the absence of demonstrable pelvic pathology. The alternatives which I suggested were mentioned as possibilities and not as truisms.

Search for evidence of blood dyscrasia is our routine procedure in all instances of functional bleeding in young women. Careful estimation of the thyroid function, both clinically and by basal rate determinations, is also done, for we have learned that thyroid deficiency plays an important rôle in the etiology of functional hemorrhage. In our experience one-half of the adolescent hemorrhages are accompanied by hypothyroidism, and the same condition exists in approximately one-fifth of those in the third decade of life.

Dr. Novak's emphasis upon the possible association of postmenopausal hyperplasia and malignancy is important. The absence of a return of bleeding in our patients with postmenopausal hyperplasia, during periods ranging from one to twelve years after the curettage indicates, in this group at least, that the hyperplasia did not predispose to the development of carcinoma.

As to the photomicrograph which was questioned by Dr. Martzloff, it is difficult to show all the characteristics of hyperplasia in one lantern slide. I am certain, however, that should Dr. Martzloff study all of the tissue from which the questionable slide was made he would concur in my diagnosis.

OBSERVATIONS PERTINENT TO GONADOTROPIC THERAPY IN GYNECOLOGY*

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FOR the past seven years we have studied ovaries and endometriums of patients who had received injections of various gonadotropic principles. We were concerned originally with the possibility that some of the responses observed in animals might occur in the human being. Later we have tried to explain the reported instances of clinical improvement without significant histologic changes. Recent studies have been concerned primarily with responses in the anovulatory states. An attempt to employ the endometrium as an indicator of the levels of ovarian function has resulted in an alteration of our classification of endometrial patterns. These studies have suggested, in addition, an avenue which may help ascertain the required clinical dose of these preparations. Attempts at therapy are influenced by various factors which may include the age of the patient, and associated pelvic conditions as well as individual receptivity.

The term "gonadotropic principle" designates certain substances that have characteristic effects on the gonads of test animals. There is no identical response in any two species. There are at least two classes of these principles: (1) the true anterior pituitary gonadotropic principle which may have its derivation directly from the anterior lobe of the pituitary or indirectly from the serum of the pregnant mare; (2) and another group derived either from pregnancy urine or from the placenta, such principles being designated anterior pituitary-like gonadotropic. The pharmacologic action of these two classes is not the same. There is evidence that the anterior pituitary-like principle is active only in an animal with an intact pituitary, while the one from the anterior lobe produces ovarian changes in the hypophysectomized animal, apparently substituting for the absent pituitary. Basic chemistry of the gonadotropic principles has not progressed in a manner comparable to that of the ovarian and testicular hormones. These gonadotropic principles are not available in pure form, but contain various contaminants. It is believed generally that these substances are of complex protein nature. Some few investigators count as many as six gonadotropic principles from the anterior pituitary, but the majority of workers believe that, perhaps, the total number of hormones actually elaborated by the anterior lobe is less than this figure.

*Presented by invitation, at the Sixty-Second Annual Meeting of The American Gynecological Society, Swampscott, Mass., May 31 to June 2, 1937.

The employment of trade names which often do not indicate the source of these preparations and the use of varying units for the expression of potency have led to much confusion in the minds of clinicians. There are three methods which are used generally by American pharmaceutical concerns to estimate gonadotropic function and in which the female immature mouse or rat is employed. The ovaries may be observed directly for evidence of follicle stimulation or information may be gained indirectly by vaginal smears to determine the onset of estrus. The ovaries may be observed directly for evidence of luteinization, or the ovaries may be weighed and weight changes regarded as evidence of gonadotropic effect. There is no definite relationship between weight increase, the induction of vaginal estrus, and the luteinizing effect. As a further source of confusion, some products are available in rat units and some in mouse units. There is some disagreement in the relationship between these units. Van Dyke quotes a ratio between a mouse and rat unit as 1 to 4, while Zondek believes it to be 1 to 6 or 8. Since these principles are used clinically most often in an attempt to produce luteinization and since the corpus luteum unit is employed most frequently, this unit has been adopted by us as a common denominator for gonadotropic activity. It is our practice to reassay the extracts which we use in terms of this corpus luteum formation unit. Such a practice has resulted in some interesting observations. In a preparation that contained 8,000 vaginal estrus rat units per c.c., we found only 200 corpus luteum rat units. In a preparation that was said to contain 2,000 luteinizing units per c.c. determined by microscopic study of the ovaries, we found only 200 corpus luteum rat units by the method of gross dissection.

METHODS OF STUDY

With differences in response so apparent in the various laboratory animals, a study of human ovaries following the administration of gonadotropic principles obtained from placenta and pregnancy urine seemed justified. The rather general use clinically of certain such commercial preparations and the equivocal results reported by many seemed to urge a careful consideration of the possible method of action, if any, of such preparations. With the various hemorrhagic and lutein changes seen in the ovaries of rodents in mind, we were led at the early part of this study to question the possibility of serious damage to the human ovary from such administrations.

In the human being some opportunities are present which may permit an insight into the ovarian effects of these gonadotropic principles.[1] We would expect to find these principles in the blood and urine of the newborn. Engle[2] has shown this to be true. Gonadotropic principles are present in pregnancy. The works of Evans[3] and of Browne,[4] especially the quantitative aspects, have been most enlightening. Evans found a consistent early "peak phenomenon" in normal pregnancy. The highest daily urinary output at this peak in one instance was 1,040,000 R. U. and the lowest was 75,000 R. U. This peak is reached rapidly and is usually highest at about the thirtieth day after their appearance. By the sixty-fifth day, the concentration is usually below 10,000 R. U. and approximates this figure for the remainder of pregnancy. These observations necessitate a careful interpretation in instances where

hydatidiform mole or chorionepithelioma is suspected, since these two abnormalities of pregnancy show consistent high concentrations of gonadotropic principles. One must feel certain of the length of pregnancy before a correct inference can be drawn. George Van S. Smith[5] has reported an increase of these principles in pre-eclampsia and eclampsia. One expects an increased production of true pituitary gonadotropic principles in hyperpituitarism. We know that these are excreted in the urine following the menopause, but here, of course, the depressing effect of the ovary on the pituitary has been removed in part.

On reviewing all these factors, we find reported little evidence of change in the ovaries. The ovaries of women dying of eclampsia or during pregnancy show no increased degree of luteinization over that in the normal pregnant states. Multiple

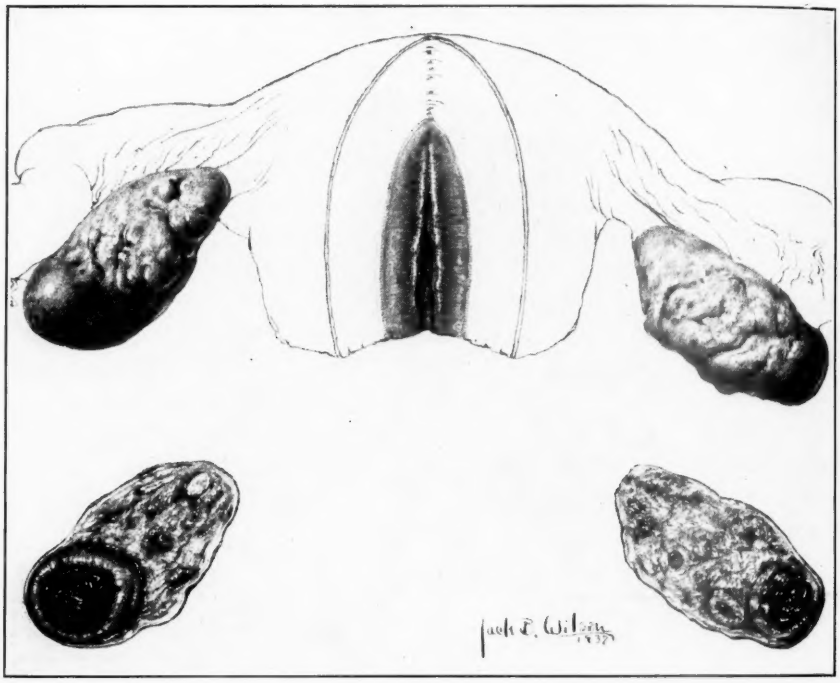

Fig. 1.—Case 1. Patient with regular menses who received 5,250 R. U. gonadotropic principle of pregnancy urine and was operated upon during the third week of the cycle. Ovaries showed three corpora lutea. A biopsy of the endometrium before treatment was begun showed an early progestational effect. This is the artist's drawing of the specimen after operation. Where the ovaries were studied only at operation, a similar drawing was made and became a part of the record. (×40.)

cysts are reported in hydatidiform mole and chorionepithelioma, but this finding is not constant. Most of the patients with pituitary tumors are seen in the later hypopituitary stage where there is little chance for hyperluteinization. Wagner[6] reports the presence of multiple lutein cysts of the ovaries and of progestational endometrium associated with amenorrhea in a woman who had a tumor of the pars glandularis of the pituitary.

Another method of study which has the advantage of being fairly well controlled is that of studying the ovarian responses after injections of gonadotropic principles. The effect may be evaluated by direct observation and study at laparotomy of ovaries following such treatment (Fig. 1); by indirect interpretation of ovarian

function from endometrial studies (Fig. 2); and by the clinical responses to such therapy of certain patients with hypogonadal syndromes and hypofunctioning ovarian states.

J. S. L. Browne has been able to estimate the progestin excretion by determining the pregnandiol content of the urine. This product represents a conjugated inactive form of progestin which does not respond to the biologic tests, but which may be precipitated and actually weighed. An employment of such pregnandiol estimations after gonadotropic therapy would probably be another method of arriving at information regarding the luteinizing effects of these principles.

In the past blood and urine hormone assays in the so-called hypo-functioning states, before and after therapy, have yielded little information of value regarding the clinical effectiveness of these principles.

The electric potentiometer method as employed by Allen and coworkers[7] for evidence of ovulation is certainly conclusive in animals but, as yet, its clinical employment has not been described. The work of Knaus[8] on manometric studies of the

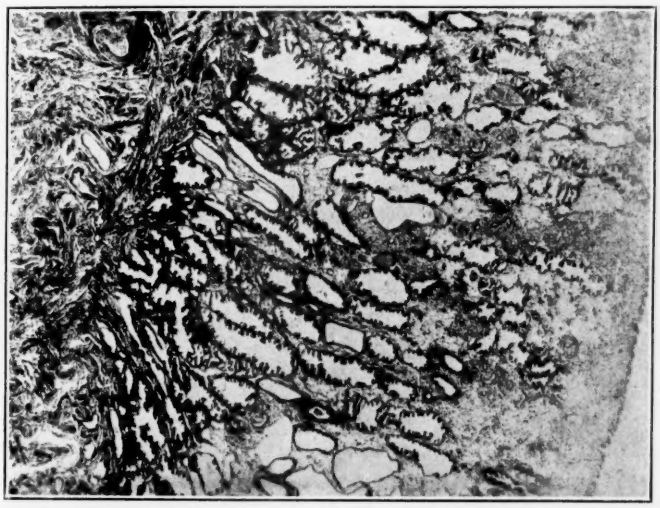

Fig. 2.—This is the endometrial picture of Case 1 after therapy. Here the menstrual history of ovarian response and endometrial pattern are in agreement. The endometrium here was taken from the uterus after operation. If the uterus had not been removed, the endometrium would have been studied by curettement. (×40.)

uterus might permit another index as to the occurrence of ovulation and corpus luteum formation. The recent work of Kurzrok and coworkers,[9] however, has thrown doubt on the so-called quiet stage in uterine contractility in the nonpregnant uterus. In their hands progesterone was observed at times to produce uterine contractions. In both of these experiments there is a valid objection to having a foreign body in the uterus.

DISCUSSION

We have been seven years accumulating data for this study. A report dealing with therapy[10] suggested the need of more exact information regarding the ovarian and endometrial response to therapy. During the progress of this work several related problems presented themselves for solution. The summation of this data required a complete review of our related material. We found that some of our deductions in previous papers[11, 12] were incorrect due to a difference in

the interpretation of the endometrial pictures. Some of the endometrial patterns diagnosed as hyperplasia of the endometrium did not show this alteration. In three patients the report of corpora lutea proved to be either persistent lutein tissue or lutein cyst. One patient approaching the menopause who had hyperplasia of the endometria did show a corpus luteum. However, she had treatment over a period of several weeks, repeated vaginal examinations and two curettements. These physical factors might have encouraged ovulation.

The very definite problem of improving the patient is constant. In an effort to relieve the woman who had bleeding as a symptom and to aid in the evaluation of other methods of treatment, a program of varied therapeutic measures was instituted. The various "levels" at which therapy could be directed, the various agents that were used and the results, were reported.[13] This furnished a valuable series for comparison.

These studies re-emphasized the fact that there is a variance in the criteria for the diagnosis of hyperplasia of the endometrium. When one is endeavoring to correct the condition of irregular bleeding, one should know if the patient is bleeding because of some irregularity of the ovarian cycle. One should be familiar with the therapeutic agent that is employed and should be able to interpret the response to therapy. To help us with these factors, a study of 358 consecutive patients with functional irregularities of the menses was made. Clinical data, endometrial histology, and follow-up records were correlated. A clinical classification of functional irregularities of the menstrual cycle which emphasized etiology and which was in harmony with the present concepts of the histology, physiology, and hormonology was attempted.

As a therapeutic agent there could be two sources of benefit from the use of these principles; the stimulating effect itself and the production of estrin and progestin. To obtain a substitutional effect, one could suppose that there was some alteration of the pituitary gland or that the production of these principles during pregnancy has been stopped. Most observers will agree on the value of substitutional endocrine therapy, but the matter of gland stimulation is subject to debate. If the gonadotropic principles meet the suggestions given above, they will do more than most endocrine principles. Several clinical conditions suggest themselves as likely to be benefitted, one of which is hypogonadal syndromes which are known to be due to inadequate gonad function; if in these instances the ovary is the influencing factor, and, if it could be stimulated to normal endocrine and exocrine function, such an individual would develop into a normal sexually mature state. The same is true in certain instances of sterility. Other clinical indications would be indirect, in that they would be dependent upon the elaboration of estrin and progestin in quantities approaching normal and would be found in varying degrees when the ovary had failed in this function. Such conditions would probably have as a symptom menorrhagia, metror-

rhagia, or amenorrhea. In these conditions we should find an ideal "proving ground" for substances supposed to stimulate and luteinize the ovary. The condition of anovulatory bleeding meets the requirements for a therapeutic reaction. There is a failure in the ovarian cycle which gives both direct and indirect evidence. An agent is used and

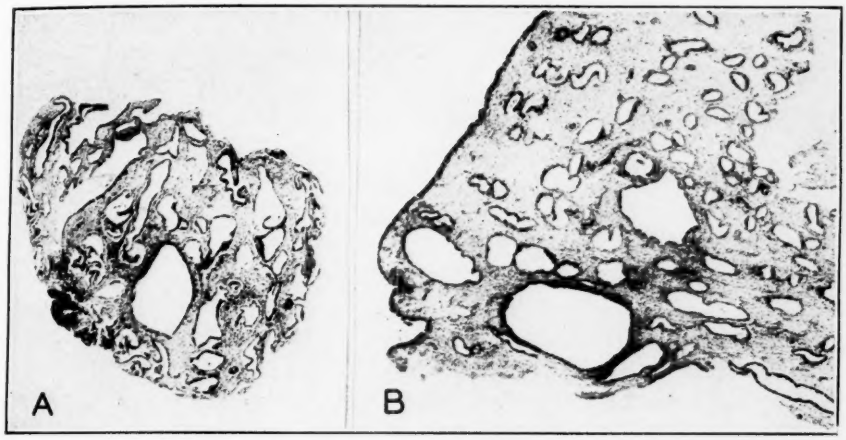

Fig. 3.—Case 2. *A*, May 4, 1937, biopsy before treatment (bleeding). *B*, May 12, 1937, curettement after treatment with 6,000 R. U. of a gonadotropic principle of pregnancy urine given on day of biopsy (not bleeding). Febrile reaction (38°) during treatment. Hyperplasia of the endometrium. No changes after therapy. These figures are representative of the tissue patterns that are obtained by biopsy technique. (×40.)

Fig. 4.—Case 3. Patient with oligomenorrhea who received 21,000 R. U. of a gonadotropic principle of pregnancy urine during the thirtieth to thirty-fourth day of her cycle. Both ovaries were available for study. These were photographed in the gross, sectioned, stained, and studied under a magnification of ×10. This figure shows two corpora lutea in the ovary. (×10.)

the characteristic effect should be forthcoming. In this instance it would be rupture of the follicle and corpus luteum formation in the ovary and characteristic endometrial changes of the progestational type. We have purposely chosen the majority of our patients from the

"anovulatory bleeding" as diagnosed by us (Fig. 3). We have examined the material scrupulously because the results are dependent upon our ability to make the diagnosis of anovulatory bleeding correctly. The therapeutic reasoning here is apparent: simply that of preventing a halt anywhere in the normal progress of maturation of the follicle and the subsequent phenomena. The chance of error lies in the frequency and facility with which the diagnosis of a primary alteration of the ovarian function is made. This has been emphasized and our method of frequent endometrial biopsies helps overcome this difficulty. We have purposely refrained from trying "augmentor" or "synergistic" effect.

Fig. 5.

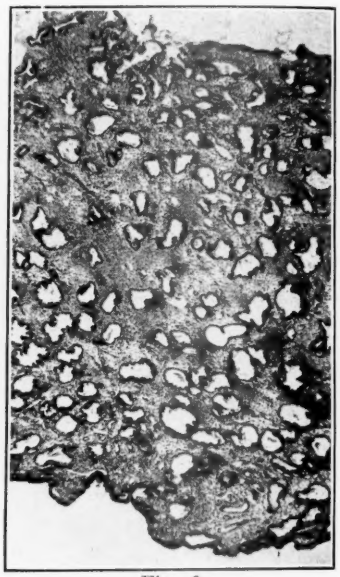

Fig. 6.

Fig. 5.—This is a higher magnification of the ovary in Case 3 which simply verifies the presence of a normal corpus luteum. (×40.)

Fig. 6.—The endometrial pattern in Case 3 which completes the study. Here we have evidence of progestational response. (×40.)

There has been no mixing of these principles with other hormones, elements, or compounds. We have simply tried to compare the effect on the human ovary and endometrium with that of the experimental animals which showed the alterations that predicated the present therapeutic concepts. We consistently used doses greater than those prescribed.

PRESENTATION OF DATA

The data which follow are obtained from observations made upon 85 patients who had received treatment with these principles. A large part of these data has been reported upon at various times. The present report is based upon a complete review and revaluation of all the

material available. More recent observations after higher dosage are included. The procedures carried out in our routine study of patients and tissues have been stated in another paper. Our method of studying the material by gross and microscopic observation and ova interpretation of changes before and after treatment is shown by the illustrations and our method of reasoning is given in the tables (Figs. 4, 5, and 6).

From the tables one can see that there has been sufficient material surveyed to warrant a fairly comprehensive study. Most of the available preparations were used. The age of the patients varied from eleven to sixty years, and the parity

TABLE I. REGULAR MENSES

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	ENDOMETRIUM AFTER TREATMENT	OVARIES
		First Week		
3	Gland	180 R. U.	Progestational phase	Corpus luteum
3	P. U.	1000 R. U.	Estrin phase	Corpus luteum
3	P. U.	1600 R. U.	Estrin phase	No observation
3	Serum	2000 M. U.	Estrin phase	No corpus luteum
		Second Week		
2	Gland	100 R. U.	Not studied	Corpus luteum
3	Gland	140 R. U.	Not studied	No corpus luteum
3	Gland	140 R. U.	Not studied	Corpus luteum
2	P. U.	800 R. U.	Progestational phase	Corpus luteum
4	P. U.	1200 R. U.	Late estrin phase	No corpus luteum
5	P. U.	1600 R. U.	Progestational phase	Corpus luteum
12	P. U.	2600 R. U.	Progestational phase	Corpus luteum
8	P. U.	2700 R. U.	Progestational phase	Corpus luteum
		Third Week		
7	Gland	360 R. U.	Not studied	Corpus luteum
8	P. U.	2400 R. U.	Progestational phase (irregular ripening)	No corpus luteum (observation grossly of ovaries)
5	P. U.	3000 R. U.	Progestational phase	Corpus luteum
9	P. U.	4000 R. U.	Progestational phase	Corpus luteum
5	P. U.	4400 R. U.	Progestational phase (marked edema)	Corpus luteum
4	Placenta	2750 R. U.	Progestational phase (irregular ripening)	Corpus luteum
4	Placenta	3000 R. U.	Progestational phase (irregular ripening)	Corpus luteum
8	Placenta	5250 R. U.	Progestational phase (irregular ripening)	Three corpora lutea
3	Serum	2000 M. U.	Progestational phase	Corpus luteum
		Fourth Week		
4	Gland	300 R. U.	Not studied	Corpus luteum
8	P. U.	2100 R. U.	Not studied	No corpus luteum (ovaries studied by inspection only)
5	P. U.	3000 R. U.	Progestational phase (irregular Menstrual phase	Corpus luteum
5	P. U.	4400 R. U.	ripening)	Corpus luteum

TABLE II

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	CLINICAL EFFECT	ENDOMETRIUM AFTER TREATMENT	OVARIES
			Amenorrhea		
4	Gland	220 R. U.	None	Not studied	No corpus luteum
4	Gland	480 R. U.	None	Phase of prolonged acyclic estrin action	Not studied
8	P. U.	2,400 R. U.	None	Curettage (no tissue available)	No corpus luteum
5	P. U.	3,000 R. U.	None	Not studied	No corpus luteum
3	Placenta	1,750 R. U.	None	Estrin arrest	No corpus luteum
			Oligomenorrhea		
4	P. U.	21,000 R. U.	(41st day of cycle)	Progestational phase (irregular ripening)	Three corpora lutea
10	Placenta	6,750 R. U.	(50th day of cycle)	Estrin arrest	Lutein cysts
			Postmenopausal		
6	Gland	300 R. U.	None	Not studied	Sclerotic ovaries
10	P. U.	5,800 R. U.	None	Estrin arrest	No corpus luteum No corpus luteum
			Premenarchal		
3	Gland	140 R. U.	None	Not studied	No corpus luteum
4	P. U.	1,600 R. U.	None	Not studied	No corpus luteum
6	P. U.	3,200 R. U.	None	Estrin arrest	No corpus luteum

was from 0 to 15. The menstrual histories extended from childhood through the regular and irregular menstrual phenomena to senility. The total material available for analysis at present includes observations upon 85 patients, distributed according to menstrual histories as follows: Regular, 22; amenorrhea and oligomenorrhea, 7; menorrhagia, metrorrhagia and polymenorrhea, 51; postmenopause, 2; and premenarche, 3. The ovaries of 57 patients were studied either grossly or grossly and

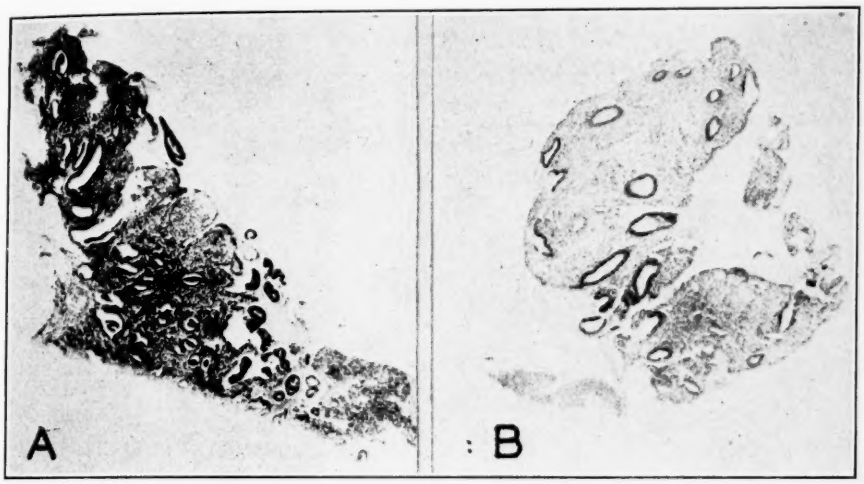

Fig. 7.—Case 5. *A*, May 17, 1937, biopsy before treatment (bleeding). *B*, May 25, 1937, curettement after 14,000 R. U. of a gonadotropic principle of pregnancy urine over a period of two days (not bleeding). Severe febrile reaction (40.4°) during treatment. No change in the endometrial pattern. (×40.)

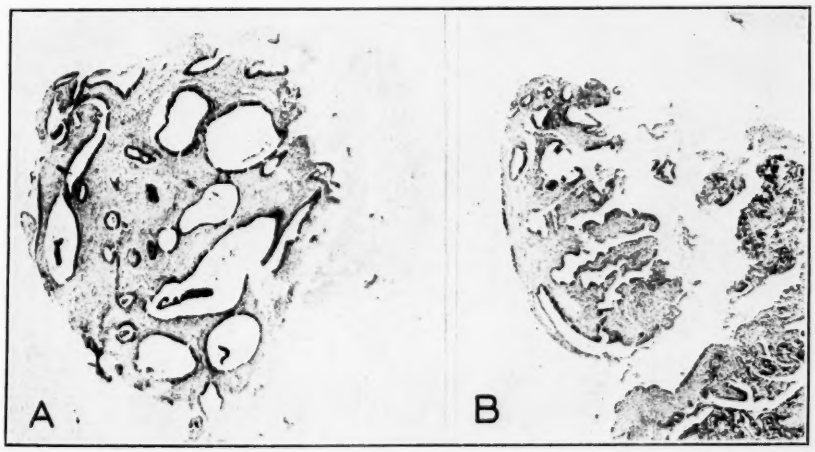

Fig. 8.—Case 4. This patient had menometrorrhagia as a symptom, and the bleeding was diagnosed as anovulatory type. She received 1,800 R. U. of gonadotropic principle of pregnancy urine. *A*, represents the endometrial biopsy before treatment (bleeding). *B*, is the curettement after treatment (still bleeding) six days later. There is some question as to the endometrial picture in *B*. We thought it was suggestive of a progestational response though the bleeding increased under therapy and a curettement was necessary. (×40.)

microscopically, while in 74 patients the endometrium was studied either alone or in conjunction with the ovaries. Gonadotropic principles from the anterior lobe or from the serum of pregnant mares were employed in 34 patients; similar principles from pregnancy urine or placenta were used in 51 patients. The total doses of the former

TABLE III

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	CLINICAL EFFECT	ENDOMETRIUM AFTER TREATMENT	OVARIES
			Menorrhagia		
3	Gland	160 R. U.	Operation	Progestational phase	Corpus luteum
3	Gland	180 R. U.	Operation*	Estrin arrest	No corpus luteum
3	Gland	180 R. U.	Operation	Estrin arrest	No corpus luteum
4	Gland	180 R. U.	None	Estrin arrest (infection)†	Corpus luteum
4	Gland	360 R. U.	None	Estrin arrest	Not studied
5	Gland	360 R. U.	None	Estrin arrest†	Corpus luteum
4	Gland	540 R. U.	Stopped	Estrin arrest	Not studied
8	P. U.	2,400 R. U.	None	Prolonged acyclic estrin phase	No corpus luteum
5	P. U.	2,800 R. U.	Operation	Estrin arrest	No corpus luteum
4	P. U.	3,000 R. U.	None	Estrin arrest, before and after treatment (infection)	Corpus luteum
8	P. U.	3,000 R. U.	None	Prolonged acyclic estrin phase	Corpus luteum cyst
4	P. U.	3,200 R. U.	None	Prolonged acyclic estrin phase	No corpus luteum
7	P. U.	6,600 R. U.	None	Prolonged acyclic estrin phase	No corpus luteum
7	P. U.	7,400 R. U.	None	Estrin arrest	No corpus luteum
9	P. U.	8,200 R. U.	None	Estrin arrest	No corpus luteum
10	P. U.	9,500 R. U.	None	Estrin arrest	No corpus luteum
5	Placenta	2,500 R. U.	Stopped	Estrin phase (menstrual phase before R)	
			Metrorrhagia		
1	Gland	60 R. U.	Operation	Estrin arrest	No corpus luteum
4	Gland	170 R. U.	Stopped	Estrin arrest	Not studied
6	Gland	180 R. U.	Operation	Estrin arrest	No corpus luteum
4	Gland	240 R. U.	None	Estrin arrest	Not studied
3	Gland	270 R. U.	None	Menstrual phase (before and after R)	Not studied
4	Gland	270 R. U.	None	Prolonged acyclic estrin phase (estrin arrest before R)	Not studied

*Operation (D. and C.) necessary to stop bleeding or done for diagnosis and not permitting interpretation.
†Cyclic polymenorrhea no biopsy before R.

TABLE III—CONT.

DURATION OF TREATMENT DAYS	SOURCE OF GONADOTROPIC PRINCIPLES	TOTAL DOSE	CLINICAL EFFECT	ENDOMETRIUM AFTER TREATMENT	OVARIES
			Metrorrhagia—Cont.		
6	Gland	340 R. U.	Stopped	Prolonged acyclic estrin phase	Not studied
3	Gland	350 R. U.	None	Menstrual phase‡ (irregular tissue shedding)	Not studied
6	Gland	360 R. U.	None	Prolonged acyclic estrin phase	Not studied
9	Gland	460 R. U.	None	Estrin arrest	Not studied
87	Gland	500 R. U.	None	Estrin arrest	Not studied
4	Gland	600 R. U.	Decreased	Estrin arrest	Not studied
3	Gland	800 R. U.	Stopped	Estrin arrest	Not studied
3	Gland	840 R. U.	Stopped	Prolonged acyclic estrin phase	Not studied
7	P. U.	600 R. U.	Operation	Estrin arrest	Not studied
2	P. U.	1,000 R. U.	Not bleeding	Prolonged acyclic estrin phase	Not studied
7	P. U.	1,400 R. U.	None	Prolonged acyclic estrin phase	Not studied
50	P. U.	1,800 R. U.	None	Estrin arrest	Not studied
6	P. U.	3,600 R. U.	None	Estrin arrest	Not studied
4	P. U.	4,700 R. U.	None	Endometritis	No corpus luteum
6	P. U.	5,400 R. U.	None	Progestational phase (irregular ripening, before and after ℞)	Corpus luteum
1	P. U.	6,000 R. U.	Stopped	Estrin arrest	Not studied
7	P. U.	7,000 R. U.	Increased	Prolonged acyclic estrin phase	Not studied
10	P. U.	7,000 R. U.	Slight decrease	Estrin arrest	Not studied
2	P. U.	14,000 R. U.	Slight decrease	Estrin arrest	Not studied
5	P. U.	18,000 R. U.	Little	Prolonged acyclic estrin phase	Not studied
8	P. U.	24,250 R. U.	Decreased	Estrin arrest	Not studied
2	Placenta	250 R. U.	Stopped	Estrin arrest	No corpus luteum
3	Placenta	2,000 R. U.	Stopped	Hypoestrin phase	No corpus luteum
3	Placenta	2,250 R. U.	Operation	Estrin arrest	Lutein cyst
6	Serum	4,400 M. U.	None	Prolonged acyclic estrin phase	Not studied

‡Progestational phase with irregular ripening before treatment.

TABLE IV

Preparations

1. ANTERIOR PITUITARY GONADOTROPIC
2. DANISH GONADOTROPIC SERUM
3. PLACENTAL GONADOTROPIC PRINCIPLE
4. DANISH ANTERIOR PITUITARY-LIKE PRINCIPLE
5. ANTERIOR PITUITARY-LIKE PRINCIPLE FROM PREGNANCY URINE

Age		*Parity*	
11-15	4	0	24
15-20	15	1- 3	20
21-40	48	4-15	41
41-44	15		
45-60	3		
Total	85		

Menses		*Dosage*	
Regular	22	Smallest total dose	60 rat units
Amenorrhea and oligomenorrhea	7	Largest total dose	24,250 rat units
Menorrhagia, metrorrhagia and polymenorrhea	51		
Postmenopause	2		
Premenarche	3		
Total	85		

Duration of Treatment

Shortest time of treatment	1 day
Longest time of treatment (at one period)	87 days

Method Employed for Study

Biopsy technique and curettement	74
Gross and microscopic study of ovaries	57
Endometrium following hysterectomy	32
Inspection of ovaries	4

ranged from 100 R. U. to 4,400 M. U., the daily dose varying from 20 R. U. to 800 R. U. Of the pituitary-like principles the total doses varied from 250 R. U. to 24,250 R. U., the daily dose from 100 R. U. to 8,000 R. U. The period of treatment lasted from one to eighty-seven days. The longest period of observation was two and one-half years. Four methods of administration were tried in an effort to duplicate the various phenomena: (1) small daily doses over a short period, (2) small daily doses over a long period, (3) large daily doses over a short period, and (4) large daily doses over a longer period.

Six patients with amenorrhea showed no response in the endometrium and no corpus luteum in the ovaries. The largest dose was 3,000 R. U. and the longest interval of treatment eight days. One patient with oligomenorrhea showed irregular progestational ripening and three corpora lutea after four days of treatment, beginning on the forty-first day of the cycle and totaling 21,000 R. U. Another showed no change after ten days' treatment beginning on the fiftieth day of the cycle. This is not conclusive as the first patient had a varying cycle, and we cannot claim that

the response was due to the injection (Case 3). Two postmenopausal patients showed no ovarian nor endometrial response and no menstruation. The maximum dose was 5,800 R. U. in ten days' treatment. In the three preadolescent patients who had never menstruated, there were no corpora lutea. The largest dose was 3,200 R. U. given in six days. None of them menstruated. The 22 patients with regular menses were grouped according to the week of the cycle in which the operation was performed. The largest dose was 5,250 R. U. and the longest period of treatment was twelve days. In most instances we were able to predict correctly the endometrial pattern and the histology of the ovary (Case 1). In another study we attempted to gain information as to the time of ovulation in untreated patients. Thus, we had a large number of controls and there was no appreciable variation in the ability to predict the pictures, when the week of the cycle was known in the two groups. Therefore, we can say from our observation, there was no varying of the cycle in the patient with regular menses. The ovaries of two patients showed more than one corpus luteum, but we hesitate to designate the ages of them. Fifty-one patients had menorrhagia, metrorrhagia, and polymenorrhea. The longest period of treatment at this time was ten days and the largest dose was 24,250 R. U. Bleeding stopped in six instances within three to six days, but the endometrium showed either late estrin arrest or a phase of prolonged acyclic estrin action. Eight patients were operated upon after three to five days' treatment. The ovaries were studied in 21 of the 51 patients. In 15 there were no corpora lutea present. In two there were old luteal cysts. In one a corpus estimated as "recent" with irregular progestational ripening of the endometrium was found. In three there were recent corpora lutea. Two of these had only 160 and 180 R. U. each and were operated upon on the third day. One had late estrin arrest of the endometrium, and the other had late progestational phase before therapy. In analyzing these 51 patients, we are unable to reconcile clinical response with the histologic picture. In only one (Fig. 7) or possibly two instances, did we find the endometrial pattern altered under therapy. In none of the instances where bleeding was checked did we find evidence of progestational response in the endometrium (Fig. 8). Novak has explained this apparent paradox.

In the three girls from eleven to fifteen years, we most certainly did not want to find a reaction similar to the Aschheim-Zondek test, but we found no effect that we could interpret. One would think that these cases would be ideally suited for observations dealing with maturing and stimulating factors.

Our experience in the general treatment of amenorrhea parallels that of others. By one or several combinations of a great many agents, we are able to get a patient to bleed once or twice, then the treatment becomes futile. In this group we have purposely picked only those patients who had no previous endocrinal therapy. In the above two groups and in the postmenopausal patients, we found no change in the ovaries or endometriums due to the doses of gonadotropic principles given. Clinical improvement from the use of these preparations is probably most often reported in the group of patients who have menometrorrhagia as a symptom. In this group 8 of the 51 (16 per cent) patients stopped bleeding. This figure can be equalled or bettered by any of the other treatments for uterine bleeding. The rational effect here would be the production of lutein tissue with an associated progestational reaction and shedding of the mucous membrane. In small doses we have not been able to show this. In one patient who was given

24,000 R. U., the findings were quite suggestive. This leads us to think that the desired reaction, if it occurs at all, will most likely follow large doses rapidly repeated over a fairly short period of time. We also think that the concentration and dosage must approach the requirements recognized in estrin therapy.

Certainly in this group of females between the ages of eleven and sixty, who had gynecologic complaints that required hospitalization, we should find ample opportunity for benefit and syndromes that would give visible response. Clinical improvement in a few instances was seen and recorded, but histologic response on the part of the ovaries and endometrium was most problematic.

In many women who have irregular bleeding as a symptom it has been our experience that there are often found complicating factors and that the correction of these altering conditions increases the chances for lasting relief. Altered position, altered blood and nerve supply, and abnormal anatomic and histologic changes are usually interpreted in terms of abnormal function. We feel that in the great majority of instances the pituitary is normal. In most instances the ovary receives adequate pituitary stimulation. The opportunity for failure in the ovary is greater. The more influencing factors and functions the greater chance there is for derangement. An abnormal ovary would hardly respond in a normal manner to an injected principle, and when we have a normal ovary the injected hormone is not needed. Our first fear in this problem was that we might find some harmful effect on the ovary from the use of these principles. Our present concern is finding any histologic effect from their use. Certainly in the doses that we have employed, we feel on much safer prognostic ground, when we find low-grade pelvic cellulitis, oophoritis, nutritional changes, displacements of the ovary, an abnormal uterus, low-grade infection of the ovary, and interference of ovarian blood supply or any other local cause that may influence the ovary.

SUMMARY

A discussion of these gonadotropic principles with an explanation for the confusion associated with their potency is given.

The presence of these principles in the human blood and urine under normal and abnormal circumstances is discussed.

The applicable evidence of ovulation and corpus luteum formation is reviewed.

The rationale of gonadotropic hormone therapy is given.

The data on 85 patients who were studied following injections of gonadotropic principles are presented. We have found and corrected a source of error in one of our previous reports.

Our conclusions are submitted.

CONCLUSIONS

1. In this series the patients with amenorrhea as a symptom or who were in the premenarchal or postmenopausal age showed neither clinical improvement nor gross or histologic changes of the tissue.

2. Eight patients (16 per cent) who had menometrorrhagia as a symptom showed clinical improvement, but the endometrial patterns were those of prolonged estrin effect, and we have not observed cessation of bleeding, the presence of a recent corpus luteum, and a progestational type of endometrium in any of these patients.

3. In patients with regular menses, we found an effect that could be definitely ascribed probably to the injected principles.

4. The anterior pituitary gonadotropic hormone is probably not available in a sufficiently concentrated preparation for general use.

5. In the group, which received pregnancy urine extract, we cannot escape the thought that the changes noticed are more characteristic of the pregnancy cycle than the menstrual cycle.

6. Gonadotropic hormone therapy dosage should be brought up to that of estrin therapy. The clinically effective dose, from these preparations will likely be large repeated injections over a short period, and probably the minimum dose will total about 25,000 R. U.

We have been aided in these studies by liberal supplies of gonadotropic principles made available by the following concerns: Parke, Davis & Co. (antuitrin-S and antuitrin gonadotropic); Ayerst, McKenna & Harrison (A. P. L., maturity factor, Danish anterior pituitary-like gonadotropic principle: Danish serum gonadotropic principle) and E. R. Squibb & Son (follutein). A part of the expenses of these studies has been defrayed by a grant from the Research Council of Duke University.

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DISCUSSION

DR. M. EDWARD DAVIS, CHICAGO, ILL. (by invitation).—From a great deal of experimental data upon the gonadotropic hormones a few definite conclusions can be drawn. In the first place, the anterior pituitary gland produces a hormone or hormones which are vastly different in their gonadotropic action from the anterior pituitary-like gonadotropic hormone present in such an abundance in the urine of pregnancy. In the second place, the urine of women following castration or the menopause contains a gonadotropic hormone which is almost a pure follicle stimulator and thus resembles very much the follicle-stimulating fraction of the anterior pituitary gland hormone. In the third place, in order that ovulation be produced experimentally in hypophysectomized animals, it is necessary first to produce growth of follicles by a follicle-stimulating hormone and then to administer the luteinizing fraction. If the latter is not given, mature follicles do not ovulate but undergo retrogression. Successful experiments in the production of experimental ovulation in monkeys have been reported by Hisaw and his group and Christian Hamburger.

Up to the present, no successful artificial ovulation has been reported in the human female. This physiologic process which can be duplicated experimentally with relative ease in laboratory animals has been difficult to carry out in the human species. It is obvious that the production of ovulation is necessary for the completion of the normal cycle. Undoubtedly many pathologic conditions seen in women are the result of, or are influenced by, the absence of ovulation.

About a year ago we became interested in a gonadotropic hormone derived from the blood serum of pregnant mares. Cole and Hart observed that during a limited period of pregnancy in mares there is present in high concentration a gonad-stimulating substance. The concentration reaches its maximum at about the sixty-fifth to the seventieth day of the gestation. Biologic studies on this substance have established distinct differences between it and other gonad-stimulating substances. It is not excreted in the urine of the mare at any time during pregnancy. It is not ultrafiltrable through collodion membranes, as is pregnancy urine substance, and it is therefore probably of a higher molecular weight. In general, it closely resembles in its gonadotropic activity the extracts of the anterior hypophysis. Thus, it was found that ovulation could be produced in young ewes during the estrus season and that a second dose of serum given seventeen days later resulted in a second ovulation with estrus which was followed by pregnancy when the ewes were mated. Similarly, mare serum injected in young sows produced ovulation and estrus, and, when the animals were bred, pregnancy followed. From these and many other experiments one can conclude that the gonadotropic hormone obtained from pregnant mare serum will cause follicular growth and luteinization with little or no degenerative changes in the ovary, so that it closely resembles the hormone derived from the anterior pituitary gland.

Cartland of the Upjohn Laboratories has successfully purified the gonadotropic mare serum substance so that the protein fraction has been almost eliminated. Furthermore, they have standardized the dose so that the rat unit represents the amount of hormone which, when divided into three daily subcutaneous doses and injected into twenty-one- to twenty-three-day-old female rats weighing 30 to 40 gm., will produce at autopsy on the fifth day a pair of ovaries weighing 65 mg., which is 5 times the weight of the ovaries in the uninjected controls. Experiments on gonadotropic hormone by Snyder and associates and in our own clinic demonstrate the great desirability of administering a gonadotropic substance intravenously in order to produce ovulation. The former authors demonstrated that it was exceedingly difficult to produce ovulation in the rabbit early in pregnancy except with large doses of gonadotropic hormone intravenously.

We administered gonadotropic hormone from mare serum intravenously in varying doses to over 50 women who were to be subjected to laparotomy for a variety of pathologic conditions. We varied the time interval so that we could learn the effect of this substance at various times in the cycle. Before the substance was administered the patient was carefully skin-tested to avoid the possibility of an anaphylactic reaction and we have had no undesirable effects. At the time of operation one or both ovaries were removed along with the diseased process. Although most of our patients were at or near the menopause and their pelvic genitalia distinctly abnormal, nevertheless the results of this study were gratifying. We found that ovulation had occurred in about one-half of the patients injected. In a number of patients two and even three ovulations were present. It may be of interest to note the fact that most of the fresh ovulations occurred between the fifth and the twelfth day and the seventeenth and the twenty-third day of the cycle. In three patients who had no regular cyclical bleeding but metrorrhagia and in whom the endometria showed no evidence of proliferation or secretion, recent ovulations were present. Furthermore, in three patients who had a glandular hyperplasia of the endometrium no ovulation could be produced.

In addition to ovulation, the most characteristic finding in the ovaries was follicle growth and some luteinization, the former being more pronounced than the latter. As Ross and Hamblen have indicated in their paper, the gross appearance of corpora lutea does not often reveal their age. It is necessary to obtain histologic sections to determine this point. These artificial corpora lutea appear histologically to resemble those produced physiologically. It is surprising, however, how few illustrations of very early corpora lutea, hours old, appear in the literature. We will publish a comprehensive study of the development of the corpus luteum in the near future.

Another interesting observation is the rapidity with which ovulation occurs as a result of this artificial stimulus. In the majority of our cases, ovaries removed eighteen to thirty-six hours following the administration of the gonadotropic substance show ovulation. This fact fits in very well with what has been observed in experimental animals.

DR. EMIL NOVAK, BALTIMORE, MD.—When dealing with disturbances of ovulation, we are faced with our ignorance of the hormone factors responsible for ovulation. The best evidence is that rupture of the follicle is brought about by a delicate quantitative balance between the follicle-ripening and luteinizing principles of the pituitary. As this balance is evidently an individual one for different individuals, Dr. Ross' negative results are not surprising, especially since there can be no certainty as to the purely gonadotropic effects of the preparations available for use.

In our very first paper on the employment of the pregnancy urine principles in the treatment of functional uterine bleeding, we emphasized the fact that the good results frequently observed could scarcely be due to the production of luteinization in the ovary. Later we had frequent opportunity of studying both the ovaries and the endometrium of patients so treated, and this confirmed our belief as to the almost complete absence of histologic changes, even though the bleeding would often be checked. Since then many others have made similar observations. The conclusion which I have drawn from this, as well as from other clinical observations, is that histologic changes are no criterion of the bleeding capacities of an endometrium. Either excessive bleeding or complete amenorrhea may be associated with almost any type of endometrium. Hyperplasia, for example, represents only a maximum growth effect of estrone upon the particular endometrium in question, but such an endometrium does not necessarily bleed, for the "bleeding level" of different endometriums differs just as does the sugar tolerance of different individuals. In some

a spill of sugar into the urine occurs at a relatively low blood sugar level, but if the sugar tolerance is high, such a spill occurs only at much higher levels. The factor regulating the bleeding spill of the endometrium is quite certainly the quantitative hormonal interrelationship between the ovaries and the pituitary.

We have been somewhat encouraged by our experience with the gonadotropic preparation made from the blood serum of pregnant mares, the same preparation as that which Dr. Ross has employed. It is much too early to speak of the results, and we are prepared for later disappointment if it comes. If and when we find it possible to bring about ovulation by endocrine treatment, as I firmly believe we shall be able to do in the not very distant future, an enormous advance will have been made, not only in the treatment of anovulatory sterility, but also of the common type of functional bleeding, which is likewise dependent primarily upon a failure of ovulation.

DR. KARL H. MARTZLOFF, PORTLAND, OREGON.—Dr. Ross mentioned the importance of obtaining endometrial biopsies. Will he please describe briefly in closing what biopsy technic was used in his study?

DR. J. L. FRAENKEL, NEW YORK CITY (BRESLAU).—The normal effects of the hormones develop and retrogress. If the corpus luteum persists, there develops a pathologic condition. The gonadotropic hormones cause the development of many follicles simultaneously in the lower animals and many corpora lutea develop. The ovary becomes full of them and they may retrogress slowly—in rats not for five months. One can thus produce sterilization in place of stimulation. Hence one must be very careful in his therapy, and should use the hormones therapeutically, only in small doses and not over a long time.

DR. ROSS (closing).—We resort to frequent endometrial biopsies to aid in the diagnosis of anovulatory bleeding and to determine evidence of progestational response. It so happens that we use the Burch forceps technic, though Dr. Novak's suction curette would answer the purpose equally as well. We take into consideration the work of Bartelmez and endeavor to explain progestational reaction of the endometrium when it is found.

If a portion of the ovary cannot be obtained, we have the significant areas drawn at laparotomy. If a portion of the ovary is obtained, we select that area which is more likely to show partial evidence. It is photographed in the gross under a dissecting microscope and under low power.

A study of our tables will show a duplication of some of the findings which Dr. Davis has described. Where we have a regular cycle, we are likely to find evidence which may be interpreted as an exaggerated gonadotropic effect. We consider the presence of a progestational reaction of the endometrium and the presence of a recent corpus luteum in the ovary of a patient who has been proved to have an anovulatory state as evidence of gonadotropic effect. The best test for these substances is found in this type of patient.

A STUDY OF THE HORMONAL CONTENT OF OVARIAN CYST FLUIDS*

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THE purpose of this investigation has been to determine the presence of and variation in the concentration of the estrogenic hormone in the fluid content of various types of genital cysts and to discover the relationship between the hormone and the secretory cells of the cysts.

A study has been made of 229 fluids from various types of adnexal cystic tumors and an attempt made to correlate the estrogenic hormonal content with the histologic findings.

Among those workers who have reported observations of the estrogenic hormone content of cyst fluids, Moulonguet and later Philipp have tried to correlate the hormonal content with the histology of the cysts.

The classification of ovarian tumors is notoriously unsatisfactory and unscientific, and we are not attempting to establish one, but for the purpose of clarity it has been necessary to adopt one which was adapted to our present needs. The following classification will be used for this report:

TABLE I. CLASSIFICATION OF CYSTIC ADNEXAL TUMORS

Ovarian cysts (97)	
Single type (76)	
Follicle (13)	Fig. 1
Corpus luteum (10)	Fig. 2
Simple serous (26)	Fig. 3
Papillary serous (6)	Fig. 4
Papillary pseudomucinous (15)	Fig. 5
Dermoid (2)	
Miscellaneous (4)	Figs. 6, 7, 8, 9
Multiple type (12)	Fig. 10
Bilateral type (9)	
Ovarian cysts associated with malignancy (8)	Figs. 11, 12
Ovarian cysts associated with pregnancy (16)	Fig. 13
Embryologic rests (8)	Fig. 14
Endometrial-like rests (3)	
Inflammatory (2)	
Cystic fibromyomas (2)	

The accompanying illustrations will give the reader an idea of the morphology of each type. It was not possible to fit each and every tumor into an exact pigeonhole, but this was done as accurately as possible by their gross and minute morphology.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

This work has been done under a grant from the Douglas Smith Foundation for Medical Research of The University of Chicago.

Fig. 1.—Follicle cyst.

Fig. 2.—Corpus luteum cyst.

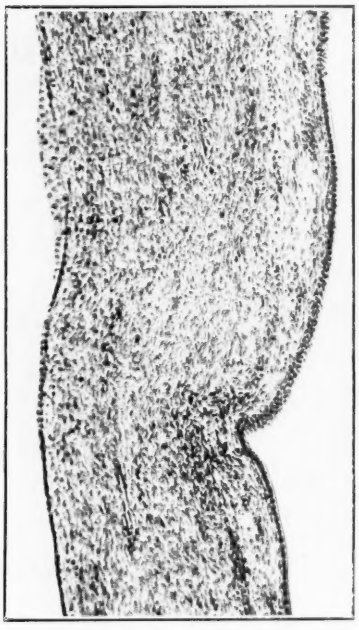

Fig. 3.—Simple serous cyst.

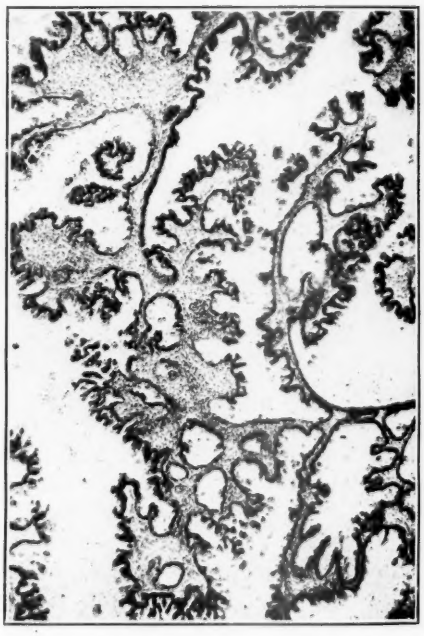

Fig. 4.—Papillary serous cyst.

One must recognize those tumors which are derived from ovarian tissue and those which are not, those which arise from secretory types of cells and those which do not.

Fig. 5.—Papillary pseudomucinous cyst.

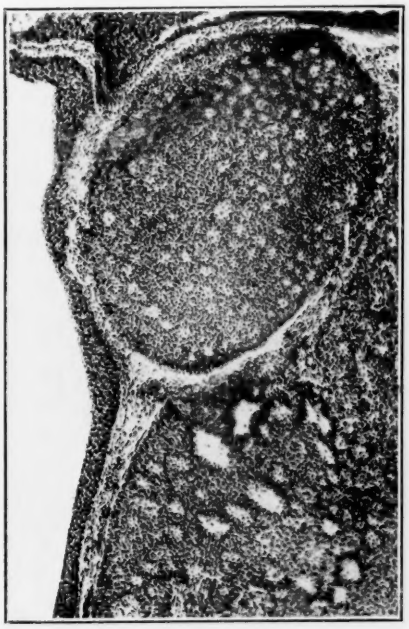

Fig. 6.—Granulosa cell cyst.

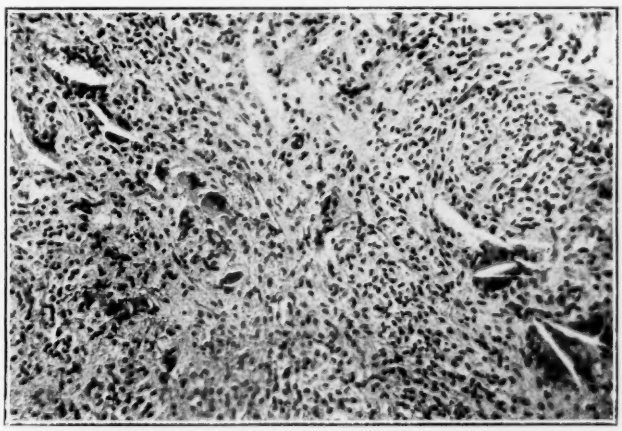

Fig. 7.—Cyst with cholesterol crystals.

Cysts are not always single, but they usually are—this type includes those unilateral tumors of one type from which one type of fluid was obtained.

The multiple type includes unilateral ovarian cysts representing more than one type of cyst and more than one type of fluid.

The bilateral group includes cases in which the cysts present on both sides were either single- or multiple-type cysts.

Separate consideration is given to malignant cystic tumors and to those cysts which were associated with a pregnancy.

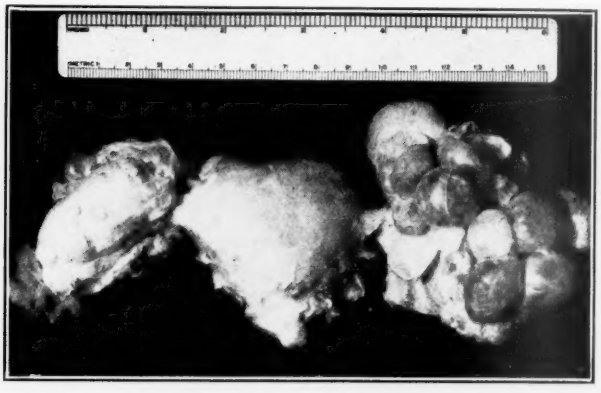

Fig. 8.—Multiple bilateral cysts.

Fig. 9.—Microscopic appearance of multiple bilateral cysts.

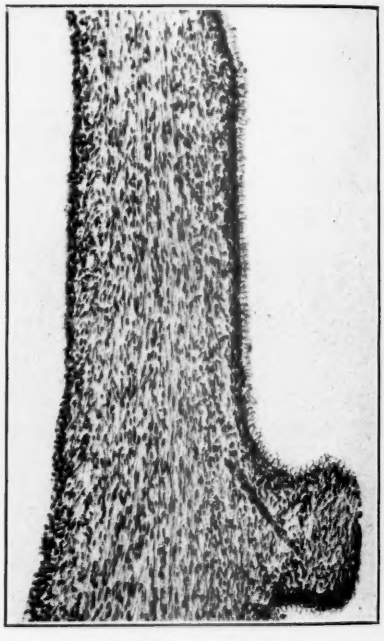

Fig. 10.—Multiple type ovarian cyst.

The nonovarian group includes those cystic neoplasms which were thought to arise from embryologic rests, from endometrial-like tissue, and from inflammatory processes and cystic fibromyomas.

The present report is based on an investigation of 158 cases of cystic genital tumors in which a histologic study and an estrogenic hormone analysis have been run in parallel.

The tissue specimens have been prepared by formalin and celloidin technic, stained with hematoxylin-eosin, and classified particularly from the appearance of the lining cells.

Fig. 11.—Ovarian cyst associated with malignancy.

Fig. 12.—Ovarian cyst associated with malignancy.

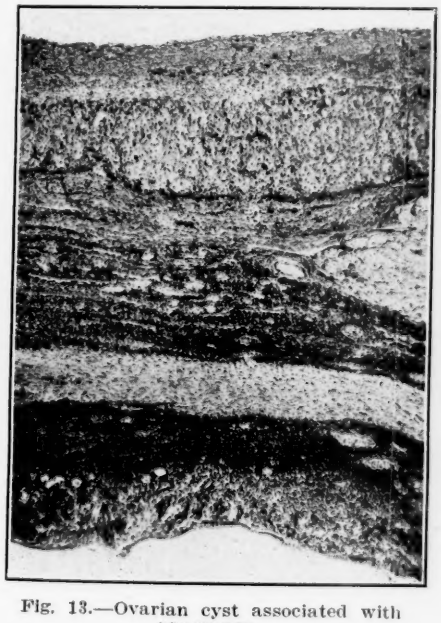

Fig. 13.—Ovarian cyst associated with pregnancy.

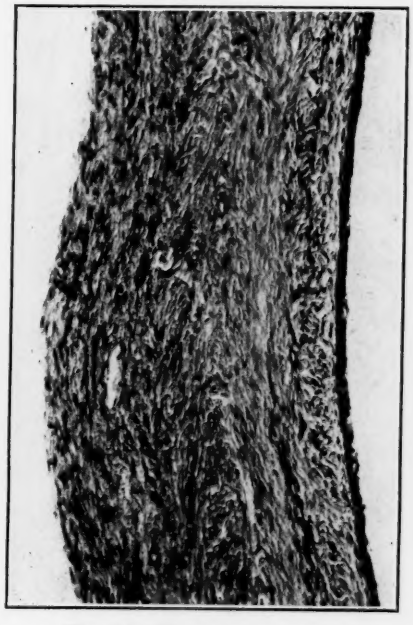

Fig. 14.—Embryonic rests.

The cyst fluids have been tested for estrogenic hormone in castrated adult rats. Vaginal cornification has been used as the criterion of a positive test. The fluids have been administered either without extraction in 3 doses (in one day) or in one dose in oil after they had been concentrated by the alcohol and ether extraction method.* The maximum dose was equivalent to 200 c.c. of fluid or less, depending upon the size of

TABLE II. OCCURRENCE OF ESTROGENIC HORMONE IN CYSTIC ADNEXAL TUMORS

OBSERVER	NO.	TYPE OF CYST	AMOUNT FLUID TESTED (C.C.)	HORMONE	
				+	-
Moulonguet, Frank, Burch, Kleine, Philipp	12	Follicle	1-5	11	1?
Moulonguet, Frank, Kleine, Philipp, Geist, Probstner	12	Corpus luteum	0.5-4	8	4
Frank, Philipp	18	Simple serous	1, 3	1	17
Frank, Kleine, Philipp	> 3	Papillary	3	0	> 3
Frank, Kleine, Philipp	> 8	Pseudomucinous	1.5, 3	1	> 7
Kleine, Philipp	> 3	Dermoid	1.5, 3	1	> 2
Wagner	1	Granulosa	0.3	1	0
Philipp	1	Necrotic	3	1	0
Moulonguet, Kleine, Biskind	7	Unclassified	1.5-15 (?)	5	2
Moulonguet, Philipp	3	Corpus luteum, pregnancy	0.5, 3	1	2
Philipp	1	Serous, pregnancy	3	1	0
Philipp	1	Pseudomucinous, pregnancy	3	1	0
Probstner	1	Corpus luteum, hydatid mole	?	1	0
Kleine	1	Carcinoma	1.5	0	1
Philipp	5	Chocolate	3	0	5
Philipp	2	Adnexal	3	0	2
Moulonguet, Dierks, Frank, Kleine, Philipp	>12	Embryologic	1-3	0	>12
Philipp	1	Parovarian, pregnancy	3	1	0

the cyst. Extractions were made in triplicate wherever the quantity of material permitted. An attempt has been made to estimate the potency of these fluids, but the limited amount of material precludes an accurate assay of most fluids.

The work summarizes nearly 2,000 tests for estrogenic hormone and approximately 600 extractions of cyst fluid.

There is a condensed summary of the work reported in the literature shown in Table II. Other reports have been omitted because the methods used did not preclude the effects of gonad-stimulating hormones. This table shows a total of 92 cysts of which 65 are ovarian, 20 non-ovarian, and 7 complicated by pregnancy or malignancy.

*Two volumes of 95 per cent alcohol were added slowly to one volume of cyst fluid. After standing overnight at room temperature the mixture was centrifuged. The supernatant fluid was decanted through a Jena glass filter. The residue was triturated twice with 95 per cent alcohol and once with ether. The supernatant fluid and the washings were combined and made acid to Congo red with hydrochloric acid. The solution was evaporated to dryness under reduced pressure. The residue was triturated with four 25 c.c. portions of anhydrous ether. The ether solution was added to a known quantity of olive oil and the ether removed.

These reports indicate that all positive cases, with the exception of one parovarian cyst associated with pregnancy, are in the ovarian group.

It is to be noted that with one exception small quantities (0.5 to 3 c.c.) of fluid were used.

In some of our cases as much as 200 c.c. of cystic fluid was used for the test.

Our cases have been analyzed from various points of view.

The age incidence in the series of 97 ovarian cysts unassociated with pregnancy or malignancy is shown in Chart 1. Most of these cysts appeared during the age of ovarian activity, 76 per cent occurring

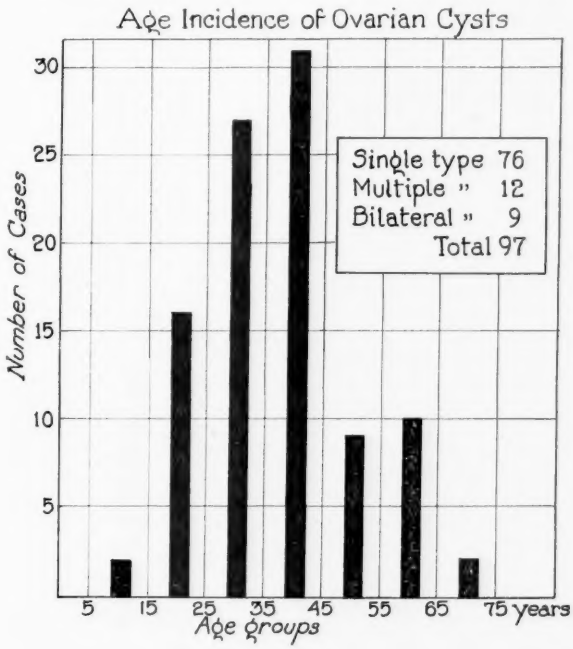

Chart 1.

between the ages of fifteen and forty-five years, and 32 per cent between the ages of thirty-five and forty-five years. About 2 per cent occurred under fifteen years and approximately 22 per cent after forty-five.

The occurrence of the estrogenic hormone and age incidence are shown in Chart 2. In this chart 76 single type-cysts are shown.

Twenty-five of 30 positive tests occurred in cysts between ages of fifteen and forty-five years, which corresponds closely to the percentage of cysts in this age group. Twenty-five positive tests occurred in 59 cases, or about 42 per cent, while 5 positive tests, or 33 per cent, occurred in those patients beyond forty-five years of age. It is noteworthy that estrogenic hormone was present in such a large percentage of cases beyond the age of forty-five years.

The relation between the type of cyst and the presence of the hormone is shown in Chart 3. About 85 per cent of the follicle, 50 per cent of the corpus luteum, 30 per cent each of the simple and the papillary serous, and about 13 per cent of the pseudomucinous cysts exhibited the presence of estrogenic hormone.

In the 8 ovarian cysts associated with malignancy, 3 showed estrogenic hormone and 5 did not.

In the 16 ovarian cysts associated with pregnancy, estrogenic hormone was present in 6 and absent in 10.

The group of cysts in which ovarian tissue was not incorporated includes 8 cysts arising from embryologic rests (parovarian, wolffian,

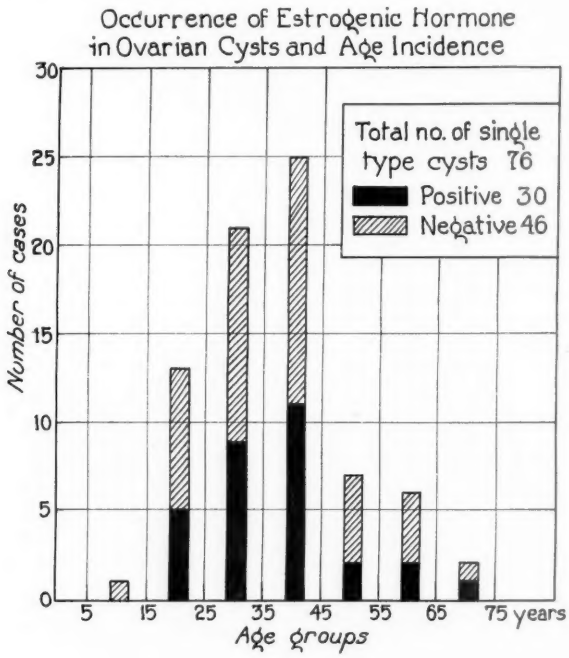

Chart 2.

hydatid), 3 arising from endometrial-like rests (chocolate cysts), 2 inflammatory cysts, and 3 cystic fibromyomas. All of these cyst fluids were negative except 2 parovarian cyst fluids, one of which was associated with pregnancy.

An attempt has been made to evaluate the significance of the presence of the estrogenic hormone in the different types of cysts by its frequency of occurrence and its potency. These findings are shown graphically in Charts 4 to 7.

Chart 4 gives a summary of 143 cyst fluids excluding those cysts which were associated with pregnancy and malignancy. The fluids have been arranged according to the type of cyst, as shown on the left

margin. The amount of fluid tested is represented on the base scale and ranges from 0.03 c.c. to 200 c.c. Note the compressed scale. Dots and circles represent individual fluids and are so placed as to denote the

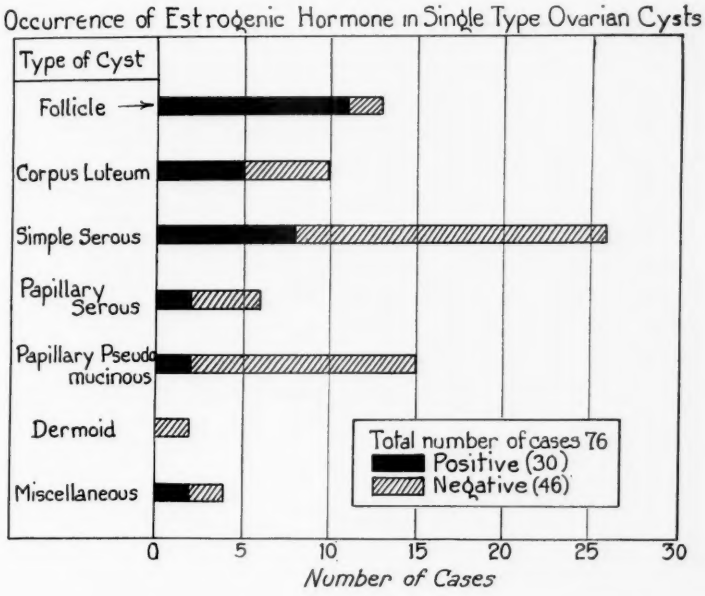

Chart 3.

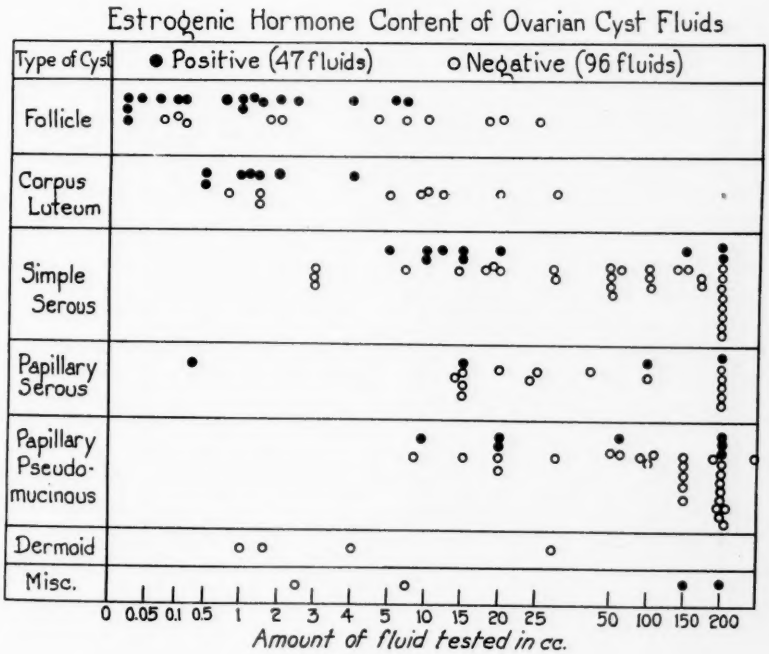

Chart 4.

amount of fluid tested for each cyst. The dots show fluids in which hormone was found, and the position of the dot shows the minimum dose at which it gave a positive test. The circles denote negative fluids, and the position of the circle indicates the maximum dose at which it was tested. At that dose either the material was exhausted or a dose equivalent to 200 c.c. of fluid had been given. For example, three follicle cysts were positive at as low a dose as 0.03 c.c., but another follicle cyst was negative at as high a dose as 25 c.c. In general, the negative values are found at dose levels equal to or greater than those at which hormone has been found in similar fluids (e.g., in the follicle and corpus luteum

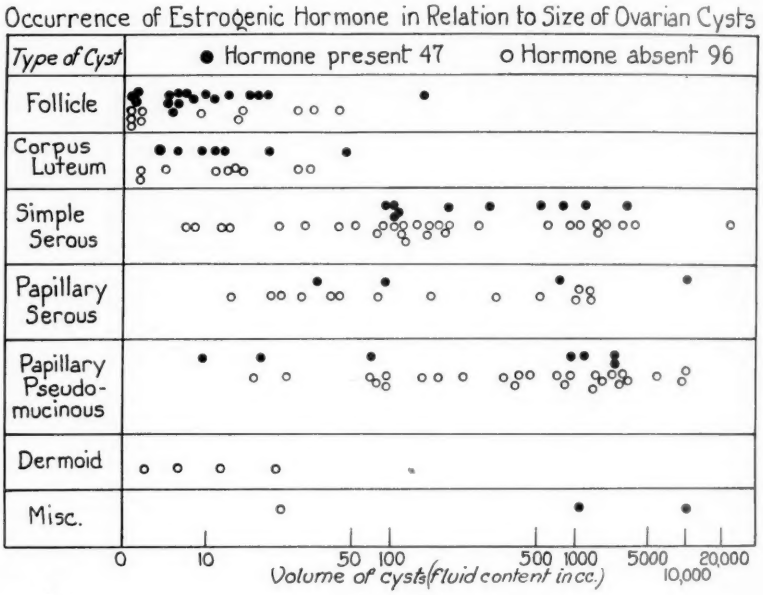

Chart 5.

groups). The chart is a summary of approximately 1,000 tests and 350 extractions. Forty-seven fluids were positive and 96 were negative.

The measured fluid content of cysts is given in Chart 5, and the variation in the presence or absence of hormone is shown. The type of cyst is shown on the left margin. The size of the cyst, in terms of the amount of fluid obtained, is shown on the base scale, which is greatly compressed because of the wide range in size (cysts as large as 22,000 c.c.). The circles and dots represent single fluids. The dots merely indicate fluids which contained hormone, and the circles, fluids which were negative. The dose levels were those shown on the previous figure. The hormone occurs in the large as well as in the small cysts, and, conversely, many small cysts are negative. It would seem that size of the cyst is not an important factor in the occurrence of hormone.

An attempt was made to calculate the total hormonal content of the cyst, and the result is depicted in Chart 6. This is the same group of ovarian cyst fluids excluding cysts associated with malignancy and pregnancy. The type of cyst is shown on the left margin. Total rat "units" are shown on the compressed horizontal scale. The dots represent positive fluids and the circles negative fluids. The "unit" is here merely an approximation of potency. For the positive fluids it has been based on the minimum dose which gave a positive response and is shown by the dots. The circles, representing negative fluids, show that less than that number of "units" was present in those particular fluids. The value was based on the highest dose tested which is dependent upon the size of the

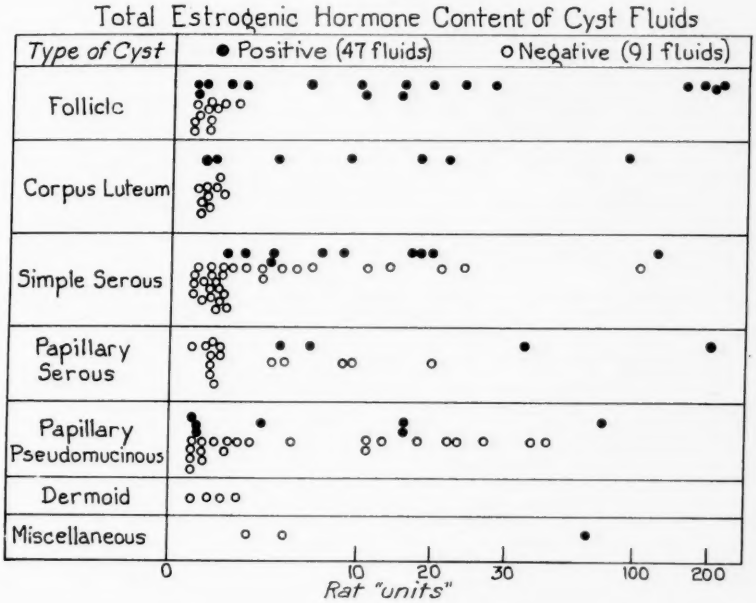

Chart 6.

cyst or the type of fluid (a maximum of 200 c.c. was tested in the large cysts). The total number of "units" in these cysts ranges from less than one to more than 200 "units." Most of the negative fluids contain less than 3 "units" per cyst, e.g., 63 per cent of 91 negative fluids contained less than 3 "units." Only 19 per cent of the positive fluids contained 3 "units" or less. In the positive fluids the total number of "units" in the different types of cysts does not seem to have a characteristic value but depends on the potency of the fluid as well as upon the size of the cyst.

The amount of hormone present per cubic centimeter of fluid seems to be characteristic for the various types of cystic fluids. This is illustrated in Chart 7. The various types are shown on the left margin. The "units" per cubic centimeter are shown on the compressed horizontal

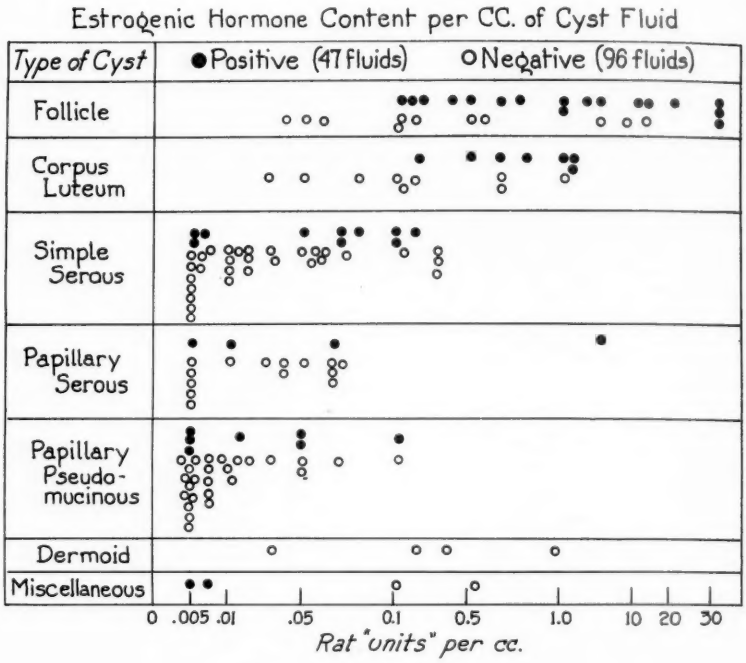

Chart 7.

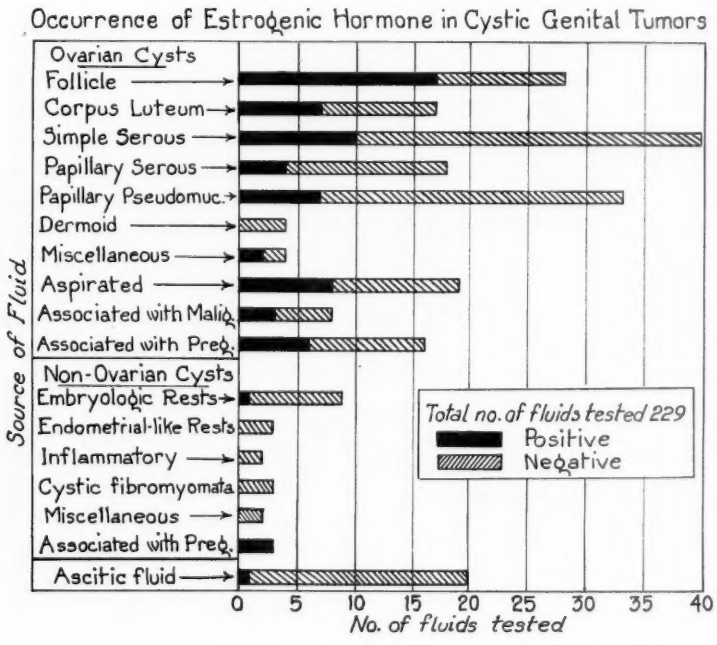

Chart 8.

scale. Dots and circles represent individual fluids. The "units" are based on the lowest positive dose, as on the previous chart. The dots represent positive fluids, and the circles represent negative fluids, that is, those which contain less than the number of "units" designated on the scale. The positive fluids range in potency from 0.005 "unit" per c.c. (i.e., a dose of the equivalent to 200 c.c. of fluid was positive) to 33 "units" per c.c. (i.e., a dose of 0.03 c.c. was positive). This range is equal to a range of 5 "units" per liter to 33,000 "units" per liter. Probably potency values below 0.05 "unit" per c.c. (i.e., the equivalent of 50 "units" per liter) are those that might be anticipated in general body fluids and tissues and are, therefore, of little significance here. Seventy-seven per cent of the positive fluids have a potency greater than 0.05 "unit" per c.c. or 50 "units" per liter. Within the group of positive fluids, fluids of different types seem to show a somewhat characteristic range of potency. Positive follicle fluids range from 0.1 "unit" per c.c. to 33 "units" per c.c. Positive corpus luteum fluids range from 0.2 "unit" per c.c. to 1.2 "units" per c.c. Positive simple serous fluids show a maximum of 0.12 "unit" per c.c.

A summarization of the findings is shown in Chart 8. The type of fluid tested is shown on the left margin. The fluids are divided into ovarian and nonovarian groups. The number of fluids is represented by the length of the bars. The solid bars show positive fluids, the cross-hatched bars the negative fluids.

Total number of ovarian fluids: 54 positive (33 per cent); 109 negative
Total number of ovarian fluids associated with malignancy: 3 positive; 5 negative
Total number of ovarian fluids associated with pregnancy: 6 positive; 10 negative
Total number of nonovarian cyst fluids: 1 positive; 18 negative
Ascitic fluids: 1 positive; 19 negative

Twenty-one cyst fluids tested for gonadotropic hormone were negative at the dose levels tested, except in special cases.

An attempt to correlate the presence of the estrogenic hormone with the menstrual cycle revealed no results which warrant conclusions at this time.

CONCLUSIONS

In some ovarian cyst fluids estrogenic hormone would seem to be found in sufficient amount to be considered of intrinsic origin, but in others in amounts which might be anticipated in body fluids in general, i.e., extrinsic.

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DISCUSSION

DR. EDWARD D. ALLEN, CHICAGO, ILL.—The most interesting point to me is Dr. Adair's finding that the endometrial cysts do not give a positive test for estrogenic hormone. We already know that the ectopic endometrium of endometriosis is responsive to hormonal change in menstruation and pregnancy and also that the menstrual blood shed from the normal uterus is high in estrogenic content.

To illustrate certain points about endometriosis, section is shown of a corpus luteum which has very definite endometrial glands far out in the lutein layer. The production of cells from the ovarian stroma is perhaps only two weeks old, so that the same stimulus has probably caused the functional growth of the lutein cells as well as this epithelium which forms typical endometrial-like glands. Whether it is the pituitary that controls this follicular stimulation or not remains to be seen. Certainly the fact that the cells in these glands are histologically perfect makes us wonder if they could possibly have been implanted, or whether they are part of a metaplasia or hyperplasia from the ovarian stroma.

DR. C. FREDERIC FLUHMANN, SAN FRANCISCO, CALIF.—From our present knowledge some of Dr. Adair's findings were predictable. For instance, the larger amounts found in follicle and corpus luteum cysts are in keeping with our belief that granulosal and thecal cells are concerned with the production of estrogen. The occurrence of estrogenic hormone in cysts in women over forty-five years of age is understandable in view of its previous demonstration in the blood and urine of such patients. I should like to ask Dr. Adair if in cases with multiple cysts the amounts of hormone in the various cysts were comparable?

As a possible explanation for variations in the amount of estrogen present in cyst fluid, I should like to suggest the possibility that the stage of the menstrual cycle at which the specimen was obtained may be of importance. It is not inconceivable that an increase may occur at the time when blood and urine normally show a rise.

DR. J. L. FRAENKEL, NEW YORK CITY (BRESLAU).—One might question whether the ovarian cysts which are occasionally seen in the newborn bring about changes in the uterus and vagina. I formerly found enormous quantities of giant cells in vaginal smears of the newborn which after about four weeks disappear. The epithelium of the older child is low, 5 to 6 cell layers deep, but in the newborn 30 to 40 cell layers deep, with 10 to 20 cell layers being cast off like the spongiosa layer of the decidua.

The witch's milk is present on the day of birth, even in prematures, and is especially frequent in negroes. Dr. Thales Martins and I have demonstrated a greater swelling of the uterus in mice that had been injected with this milk than with mother's milk. (One must extract the milk with ether, otherwise the animals die.) Thus this is not an estrogenic hormone but probably gonadotropic.

DR. EMIL NOVAK, BALTIMORE, MD.—The results of this study are about what one would expect if one takes into account the histogenesis of the various types of ovarian cyst and the assumed rôle of the living cells in the production of estrone. Normally the latter has its chief ovarian source in the follicle epithelium and probably also the theca cells, so that it is not surprising that follicle cysts are likely to be most constant and richest in their estrogenic content. The same statement may be made concerning corpus luteum cysts.

The histologic appearance of any tissue is, however, not always a good criterion of its functional activity. One of the best illustrations of this statement is to be found in the case of so-called cystic ovaries, in which the ovaries are full of many small follicular cysts. As a rule these tiny cysts represent follicles in various stages of atresia, some with epithelium still present, others in which both the ovum

and epithelium have degenerated. Such cysts would be expected to show little or no estrone activity. By contrast, in some cases of hyperplasia of the endometrium associated with functional bleeding, one may see ovaries which grossly are quite similar, but in which the granulosa and often the ova are well preserved. In this latter group one may expect to find a high degree of estrogenic activity.

In still other types of follicle cysts, usually multiple, the estrogenic activity merely reflects a relatively high degree of pituitary effect. For example, in the frequently observed cystic degeneration of conserved ovarian fragments left after resection of the ovaries, the pituitary effect seems to be concentrated on a much lessened ovarian registering board, with excessive follicle maturation in such ovarian fragments, in accordance with Lipschutz's "law of follicular constancy." This pathologic-physiologic change is probably much more frequently responsible for cystic degeneration of residual ovarian fragments than is the commonly assumed disturbance of circulation.

DR. ADAIR (closing).—The only conclusion that we felt justified in drawing was that some of these cysts apparently produced their own estrogenic hormone, and others contained an amount of estrogenic hormone which might be considered to be common to the tissues in general. With few exceptions, the cysts which we thought were not associated with ovarian tissue showed no estrogenic hormone, or at least none in high concentration.

We analyzed some of the simple type of cysts with reference to what we called the menstrual age of the cyst, that is, the time of removal in relation to the menstrual cycle. We were not able to see any relationship between the presence of the estrogenic hormone and the menstrual cycle. We do not like to draw final conclusions because our group of cases was hardly sufficient.

With reference to the presence of hormone in the multiple type of cysts, we did find variations in concentration of the estrogenic hormone. It is, however, not impossible for the fluid of one cyst to diffuse into the fluid of another. It might thus be impossible to tell about the actual source of the hormone in any given fluid.

AN EFFICIENT COMPOSITE OPERATION FOR UTERINE PROLAPSE AND ASSOCIATED PATHOLOGY*

EDWARD H. RICHARDSON, M.D., BALTIMORE, MD.

(From the Department of Gynecology of the Johns Hopkins University and Hospital)

THE more advanced grades of uterine prolapse are commonly encountered in association with hypertrophy, elongation and chronic infection of the cervix, benign disease of the corpus, pronounced descent of the bladder or cystocele, impairment of the vesical sphincter, urethrocele, a broken-down perineum and pelvic floor, rectocele and enterocele. Successful management of such complex vaginal hernias often taxes to the utmost the skill and resourcefulness of even the most experienced pelvic surgeons, for no single plan of reconstructive surgery has yet been devised which is rationally applicable either to all types or to the several age groups. Consequently, if an attempt is made to treat indiscriminately a considerable number of them according to any single stereotyped operative procedure, it will inevitably result in a disappointing percentage of only partial successes and not a few outright failures. Uniformly good end-results will be obtained only through the utilization of a comprehensive therapeutic program: one which includes first, intelligent preoperative study and preparation of the individual patient; second, the exercise of discriminating judgment in the choice of operation to be employed; and, third, diligent and enlightened postoperative care.

From the standpoint of surgical therapy alone, all patients afflicted with vaginal hernias fall naturally into two age groups; young women in whom the partial or total preservation of function is highly desirable, and older women in whom this factor becomes one of subordinate importance. A substantial majority of the advanced grade cases are encountered in the menopausal years, representing as they do the terminal consequences of repeated childbirth trauma, sustained hard work, and progressive atrophy of supporting structures. On the other hand, the lower age group, recruited in part from those whose muscular and fascial supports are congenitally defective but composed chiefly of those unfortunates who have been the victims of both economic pinch and mediocre obstetric care, are encountered altogether too frequently in every clinic. Preservation of function in these younger women always involves a decision regarding continuation of menstruation, sexual relations, and further childbearing. In arriving at this decision due consideration must be given not only to the extent of damage which the

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reproductive units and adjacent structures have suffered in consequence of trauma and associated disease but also to the individual patient's general physical condition. Other factors, too, of scarcely less importance include her social and economic status, the number of living children and the hazards of previous pregnancies and confinements.

The operations commonly employed in this younger age group include the application of conservative therapy to a damaged and infected cervix, plastic repair of the fascial bladder and urethral support often including also plication of the vesical sphincter, reconstruction of the pelvic floor, and rectovaginal septum, together with an efficient suspension of the uterus by the abdominal route. The question of permanent sterilization by resection of the uterine ends of the fallopian tubes in these women is always a pertinent and individualistic one to be decided only through judicious examination of the several factors involved. But the surgical problems presented by this group are relatively simple and the reconstructive operations required are not difficult to execute.

Much more complex by contrast are the problems with which the pelvic surgeon is confronted in the advanced stages of vaginal hernias so frequently encountered in elderly women. Collective experience has abundantly demonstrated that even simple abdominal operations are far less well borne by these patients than are the most extensive vaginal procedures. This fact, coupled with the inevitable necessity of supplementing any type of abdominal operation by extensive vaginal reconstructive work performed either simultaneously or in two stages, has led to the gradual development and advocacy of a number of excellent plans devised to reestablish adequate and permanent mechanical support for the several anatomic units involved and to eliminate any coexisting pathology.

The operations most widely employed today in the treatment of these hernias in older women are (1) total vaginal hysterectomy, performed according to individual preference for any one of several well-established methods and supplemented by central fusion and anchorage of the ligamentous stumps, high obliteration of the culdesac, reconstruction of the pubocervical and rectovaginal fascial planes and of the pelvic floor; (2) the Watkins-Schauta-Wertheim interposition operation; (3) the Manchester or Fothergill procedures; (4) the Curtis advancement operation; (5) the Neugebauer-Le Fort colpocleisis; and (6) total colpectomy.

Colpocleisis and total colpectomy appear to have grown in favor within recent years and excellent results are reported by those who have had considerable experience in their use. It seems to me, however, that they are applicable by preference only to very old, feeble women afflicted with complete procidentia or with inversion of the vagina following total hysterectomy. So that while these two operations undoubtedly possess distinct merit and have a definite field of usefulness,

they should be resorted to only in the poor surgical risk group or when there is scant likelihood of success in attempting to achieve a more normal anatomic reconstruction.

Because of uniformly satisfactory end-results obtained in private patients, my own preference for a number of years was total vaginal hysterectomy. But recent follow-up studies conducted in Dr. Cullen's clinic at the Johns Hopkins Hospital by Everett revealed the surprising fact that total vaginal hysterectomy performed by a group of experienced gynecologists for the treatment of advanced grade vaginal hernias failed to achieve complete anatomic success in 30 per cent of the cases, whereas only 4 per cent of failures occurred following the interposition operation.

But utilization of the Watkins, the Curtis, or the Manchester operation is restricted by reason of the fact that all three presuppose the existence of a normal corpus uteri which, unfortunately, is by no means always present since one frequently encounters instances of uterine prolapse in which associated pathology of the corpus demands its removal. Furthermore, even when an operation of this type may be rationally employed it must be admitted that an interposed normal uterus remains a potential focus of both benign and malignant disease, subsequent treatment of which either by surgical extirpation or irradiation involves extraordinary technical difficulties as well as greatly increased hazard of serious complications and sequelae.

It seemed to me conspicuously worth while, therefore, to construct a composite operative plan that would combine the essential features of total vaginal hysterectomy with those of the several transposition methods and at the same time would eliminate the humiliating percentage of partial failures chargeable to the former procedure as well as the potential dangers left lurking in the latter ones.

Such a plan must be comprehensive in scope having for its objective (1) riddance of the hypertrophied and diseased vaginal portion of the cervix; (2) extirpation of the corpus uteri, together with the tubes and ovaries if indicated; (3) optional destruction or excision of any remaining cervical canal epithelium; (4) minimal trauma and devitalization of structures later to be utilized for reconstruction purposes; (5) preservation of an assured and adequate blood supply to these several units; (6) total ablation of associated enterocele through high obliteration of the culdesac of Douglas; (7) rational utilization of all supporting structures that experience has demonstrated to be helpful and dependable; namely, the pubocervical fascia, the basal portions of the broad ligaments with their extraordinarily strong cervical attachments, the uterosacral and the round ligaments, the fascia of the rectovaginal septum, as well as the muscles and fascial layers of the pelvic floor and perineum; (8) reestablishment of a vagina of normal depth and caliber; and (9) restoration of normal anatomic relationships.

Now all of these requirements can be adequately met by judicious selection from such well-established vaginal operations as those discussed above, which are widely employed today in the treatment of vaginal hernias, certain of their most dependable features and combining these into a composite reconstructive plan more comprehensive in scope and of greater flexibility and efficiency than any one of the contributing models. In the operation about to be described this is precisely what I have done; consequently, no claim of originality is made in its presentation beyond that involved in the construction of what I believe to be an improved plan out of borrowed units for each one of which I hereby make grateful acknowledgement to the distinguished gynecologists who originally devised them.

One cannot too strongly emphasize the vital importance of adequate preparation of the individual patient through a period of hospitalization sufficiently long to permit completion of a general diagnostic study and the application of such fortifying therapeutic measures as it may indicate. Not uncommonly complete procidentia is associated with vulval dermatitis or other skin diseases, with gravity ulcers, with chronic infection of the cervix or with edema of the prolapsed structures and impairment of circulation. Existence of such maladies is an absolute contraindication to radical operative intervention and they must be absolutely cleared up beforehand by a period of rest in bed and intelligent general and local therapy. So also coexisting cardiovascular embarrassment, renal impairment, diabetes and obesity are frequently encountered and require a period of intensive treatment prior to operation. And, finally, a judicious choice of anesthesia must be made in accordance with the experience and convictions of the individual surgeon.

TECHNIQUE OF THE OPERATION

The Surgical Toilet.—The bladder and rectum must be empty. Scrupulous care and thoroughness must be exercised in the preliminary surgical toilet of the operative field. First, the entire pubic and vulval regions, the adjacent inner surfaces of the thighs and the perianal area must be cleanly shaved. Next a thorough washing externally over a wide circumference is done successively with green soap and warm water liberally applied, 1:1,000 solution of bichloride of mercury and 70 per cent alcohol; then follows an identical cleansing of the vagina and cervix; and, finally, a widespread and accurate application to both the vulva and vagina of Scott's solution (1 per cent acetone; 2 per cent mercurochrome; in 70 per cent alcohol). A folded sterile towel is now anchored over the anus by means of an adhesive strap securely applied across the buttocks. The upper margin of this towel is then sutured to the upper margin of the perineum and the sterile draperies are adjusted.

Step 1: Separation of the Anterior Vaginal Wall From the Bladder.—(Fig. 1.) The cervix is exposed, its anterior lip grasped with a straight Jacobs forceps and strong downward traction is made. An Allis clamp is applied to the vaginal wall in the midline 1 cm. posterior to the urethral meatus and sufficient traction upward is made upon it to flatten out the entire anterior vaginal wall. A transverse incision is now made through the vaginal wall 1 or 2 cm. above the external os and partly encircling the cervix. Straight Mayo scissors are next used to effect by blunt dissec-

tion partial separation of the anterior vaginal wall from the bladder. With the blades closed the scissors are carefully insinuated beneath the vaginal wall exactly at the midpoint of the initial transverse incision, advanced 2 or 3 cm. and the blades then separated. The segment of vaginal wall thus detached is divided along the midline. By alternate repetition of these two maneuvers completion of the vertical limb of the familiar ⊥ shaped incision to within 1 cm. of the meatus is much more

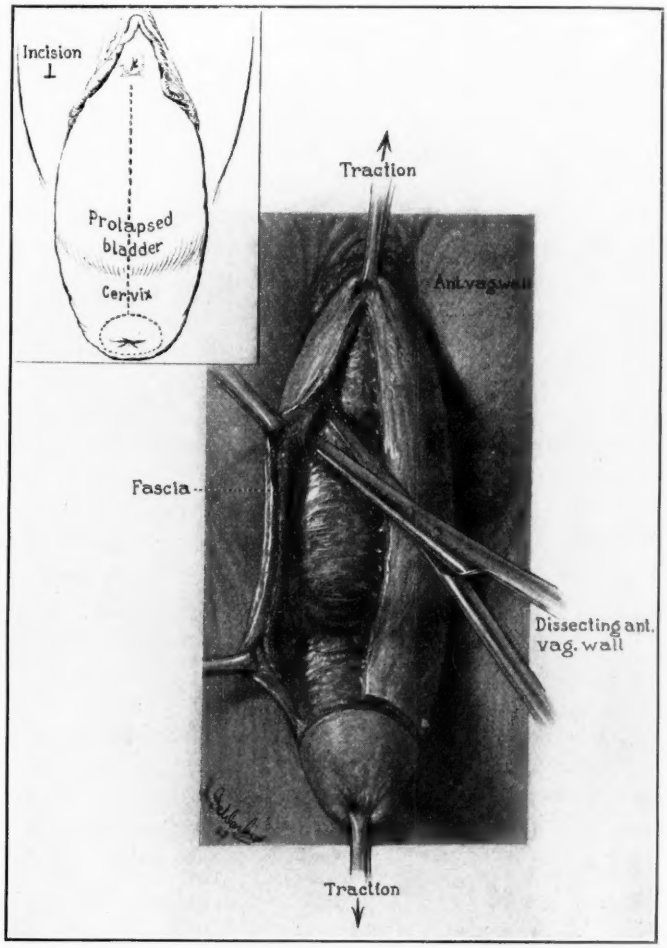

Fig. 1.—Strong traction downward on the protruding elongated cervix and upward on the vaginal wall at a point 1 cm. below the urethral meatus is maintained throughout the dissection here shown. Blunt scissors are being used to separate the bladder from the vaginal wall. The dotted line in the inset indicates the initial inverted T-shaped incision.

quickly executed than by any other method. There is no danger of puncturing the bladder if during this dissection constant traction upon the vaginal wall in opposite directions is maintained so as to obliterate all folds. The plane of cleavage between the bladder and the vaginal wall is easily located and followed.

Step 2: Dissection of the Pubocervical Fascia and of the Bladder.—(Fig. 2.) The two triangular flaps of vaginal wall thus outlined are now successively put under uniform tension by the application to their margins of several Allis clamps. Instead

then of being content simply to separate further the bladder laterally by blunt dissection, it is also possible always to obtain from each flap by careful sharp dissection a substantial and valuable layer of pubocervical fascia. Normally this structure constitutes the chief support of the bladder base and cystocele is essentially a herniation through it. Consequently, it will always be found thin and attenuated over the central zone but supplies a supporting layer of surprising thickness and tensile strength when the dissection is carried well out on each side. It merges above into the two vesicocervical fascial pillars which, in turn, fuse with the basal segments of the broad liga-

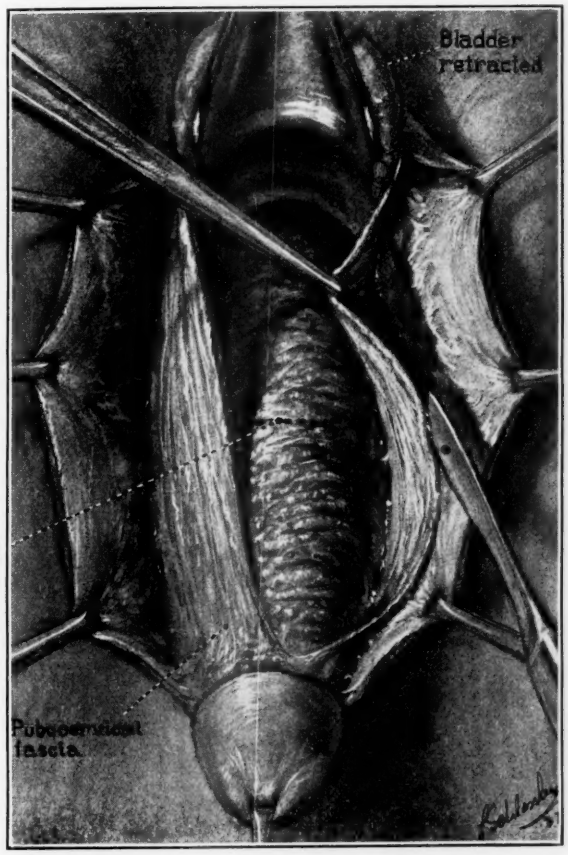

Fig 2.—After completing the separationof the vaginal wall and bladder from the elongated and hypertrophied cervix a guillotine amputation of the latter is done at the level indicated. Preliminary dissection of the pubocervical fascia from the vaginal flaps is here shown.

ments, thus furnishing two remarkably sturdy fascial bands for later approximation and anchorage to the cervical stump as presently to be described. Clean anatomic identification and utilization of this fascia is a step of prime importance in achieving permanent cure of cystocele. The bladder is next separated from the cervix also by blunt dissection initiated with Mayo scissors and continued upward with the index fingers until the vesicouterine peritoneum is freely exposed.

Step 3: Amputation of the Cervix.—The initial transverse incision is now extended to encircle completely the cervix and from the latter the vaginal cuff is quickly stripped off posteriorly and on each side quite up to the bases of the broad

ligaments, thus skeletonizing the hypertrophied and elongated portion, often 5 to 10 cm. long, which is then amputated. The cervical canal above this level is next dilated, the vaginal cuff is pared down to proper width, then fitted neatly over the

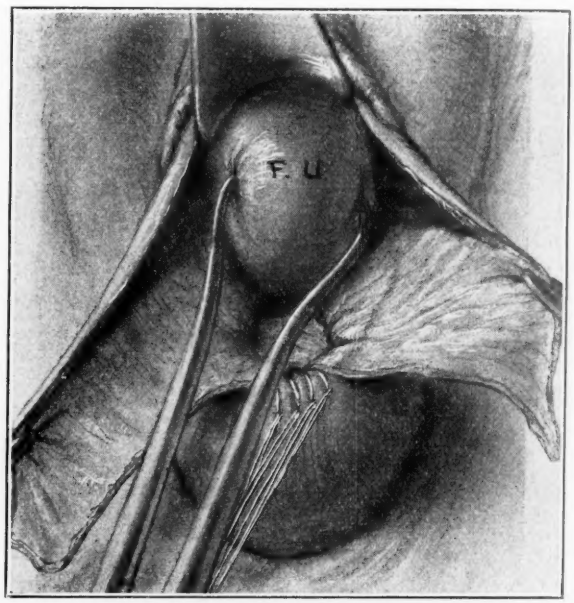

Fig. 3.—The peritoneal cavity has been opened between the uterus and the bladder and the enlarged corpus uteri is being delivered by traction.

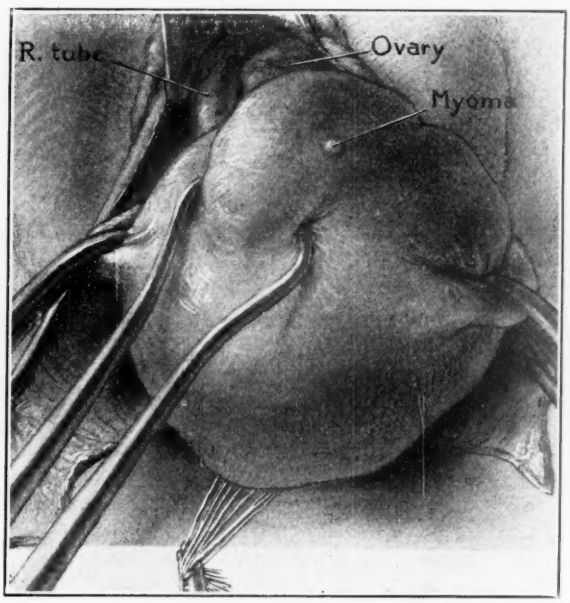

Fig. 4.—The myomatous corpus uteri is shown fully delivered. The right tube and ovary are clearly seen. A single clamp has been applied on each side to the uterine ends of the tube, the round and the uteroovarian ligaments prior to their division.

cervical stump and approximated to the canal mucosa by means of interrupted sutures of chromic catgut. The first suture should be introduced in the midline posteriorly and subsequent ones radiating from the canal like the spokes of a wheel until three-fourths of the stump is covered. The anterior one-fourth is later completed. These sutures are left long temporarily, being gathered in the bite of a single clamp as they are tied, and used for traction.

Step 4: Delivery of the Corpus Uteri.—(Figs. 3 and 4.) A retractor is now inserted beneath the bladder, traction downward being maintained upon the cervical stump by means of the sutures thus clearly exposing the vesicouterine peritoneum which is incised transversely. The same caution must be exercised here as is required in opening the peritoneum elsewhere not to cut or traumatize a loop of bowel that

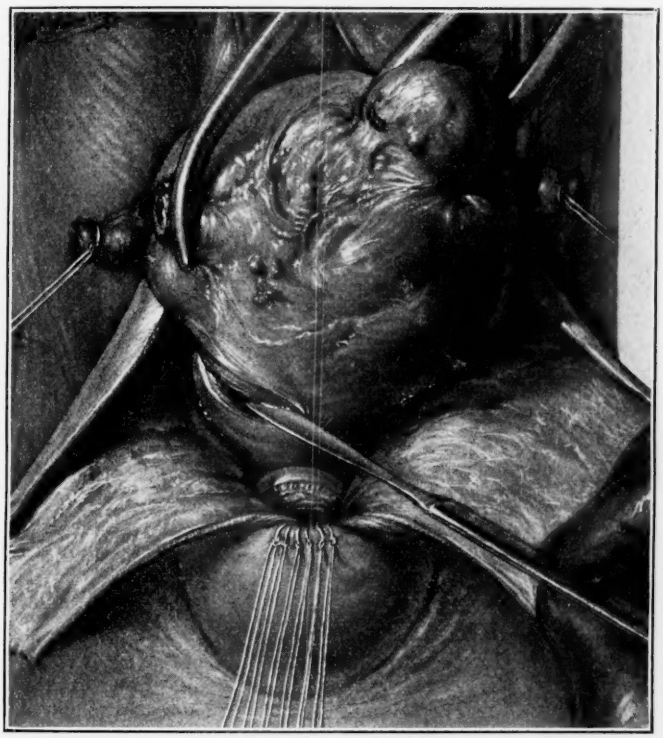

Fig. 5.—The uterine vessels have been divided at the level of the internal os and securely ligated on each side. A subtotal hysterectomy at the level of the internal os is being completed with a deep cupping of the retained cervical stump.

may be presenting just beneath. The subvesical retractor is now shifted into the peritoneal cavity and a quick exploration is made with the fingers to determine the exact status of the uterus and its appendages. Traction downward upon the cervical sutures and upward upon the intraperitoneal retractor exposes the lower segment of the anterior uterine wall through which a traction suture is passed embracing a deep, wide bite. The cervical stump is now pushed back into the posterior vaginal fornix and simultaneously a steady pull is exerted upon the uterine traction suture. This lifts the uterus forward and readily permits insertion of a second traction suture at a higher level in its anterior wall to which the pull is shifted as the first suture is withdrawn. Repetition of this device, which was suggested some years ago by T. S. Cullen, provides a simple and easy method of delivering the corpus uteri into

the vagina with far less effort, trauma and hemorrhage than if the sharp pointed forceps shown in the illustrations are used.

Step 5: Removal of the Corpus Uteri.—(Fig. 5.) A subtotal hysterectomy is now done. If the ovaries are to be removed, the infundibulopelvic ligaments are identified, adequately exposed, clamped, divided and doubly ligated with chromic catgut. If the ovaries are to be retained, two clamps are applied on each side across the uterine ends of the fallopian tube, the round and the uteroovarian ligaments between which these structures are amputated as close to the cornua as possible. The clamps on the distal stumps are now replaced by transfixing sutures of chromic catgut which are securely tied around them and left long for later traction usage. The uterine vessels are now clearly visible on each side. They are next clamped at the level of the internal os, divided and doubly ligated with chromic catgut. The cervix is now cut across at this level, being slightly cupped to permit a neater closure of it. Upon removal of the corpus, it is at once laid open for accurate inspection of both the endometrium and the myometrium. If no suspicion of malignant disease is found, the cervical stump may now be safely utilized for supporting purposes. If before

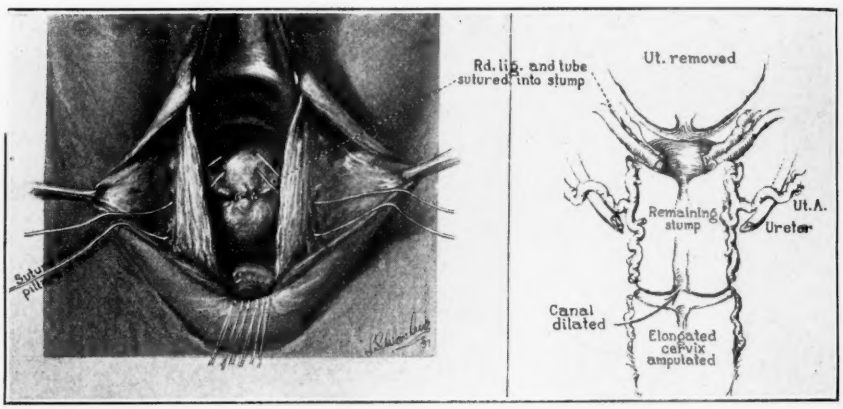

Fig. 6.—Only that segment of the uterus to which is attached on each side its major supporting structure, the basal portion of the broad ligament, remains. This is interposed beneath the bladder and securely anchored by sutures which also include and approximate the stout pillars of pubocervical fascia.

doing so, the operator prefers to get rid of the remaining canal endometrium, this may be accomplished either by cauterization or excision. I do not believe that either is necessary.

Step 6: Utilization of the Round Ligaments for Additional Support of the Cervical Stump.—We now have left that segment of the cervix to which are attached the strong basal portions of the broad ligaments and the uterosacral ligaments. Moreover, these attachments have not been traumatized nor has the normal anatomic relationship of the cervical segment to either the main trunks of the uterine vessels nor to the ureters been disturbed. The anterior and posterior margins of the cervical stump are now approximated by means of a chromic catgut suture introduced exactly in the midline, securely tied and left long for temporary traction purposes. Angle sutures of the same material are next placed on each side which first pass through the posterior margin of the cervical stump then transfix the stump of the round ligament, also that of the uteroovarian ligament if the ovaries are being retained, and finally emerge through the anterior margin of the cervical stump. When tied these sutures snugly appose the round ligaments to the angles of the cervical stump for additional support.

Step 7: Transposition of the Cervical Stump.—(Figs. 6 to 8.) At this point we utilize principles borrowed from both the Watkins and the Manchester operations. The two pillars of vesicocervical fascia so carefully isolated and preserved at the beginning of the dissection are now clearly exposed. A stout chromic catgut suture is passed beneath the left one close to its cervical attachment, care being taken to include the entire thickness of this sturdy structure, and is continued as a purse-string along the cut margin of the vesico-uterine peritoneum just beneath the bladder to the midline; here a deep and substantial bite is taken with the needle through the upper margin of the cervical stump, the suture then being further continued toward the right as a purse-string to include the remainder of the peritoneal flap and finally passes beneath the right vesicocervical fascial pillar close to its cervical attachment. When tied this suture, which is quite simple and easy to introduce, closes the peritoneal cavity, anchors the two strong fascial pillars to the cervical stump

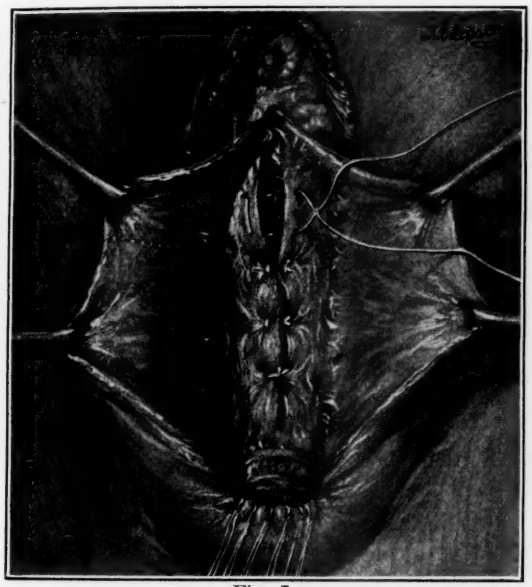

Fig. 7.

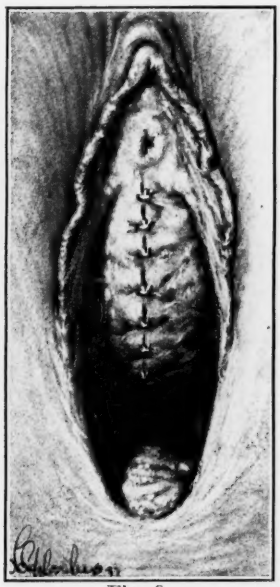

Fig. 8.

Fig. 7.—The bladder has been returned to its normal position and is now strongly supported by both the transposed cervical stump and plication of the stout pubocervical fascia.

Fig. 8.—The anterior operation completed.

in a manner similar to the Manchester technique and brings the strongly supported and well-elevated cervical stump snugly up under the bladder just as the uterine corpus is utilized for this purpose in the Watkins operation. Several mattress sutures of chromic catgut are next introduced to imbricate the vesicocervical fascia from the cervical stump forward to within 1 cm. of the urethral meatus. The two flaps of vaginal wall are then pared down to proper size and the anterior wound is neatly closed with interrupted sutures of plain catgut.

Step 8: Reconstruction of the Pelvic Floor and Perineum.—(Figs. 9 to 12.) There remains now only the broken down perineum and pelvic floor together with the commonly associated rectocele to be dealt with. An Allis clamp is applied in the midline posteriorly at the mucocutaneous border, one on each side of the vaginal introitus at the level of the lower border of the hymen and a fourth one at a midpoint of the posterior vaginal wall just above the crest of the rectocele. Simul-

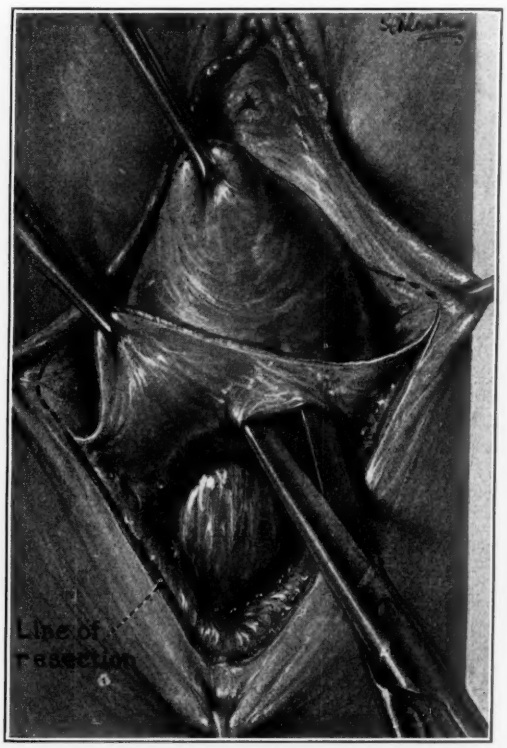

Fig. 9.—The relaxed pelvic floor and large rectocele are here shown. The dotted line indicates the area to be denuded by blunt dissection.

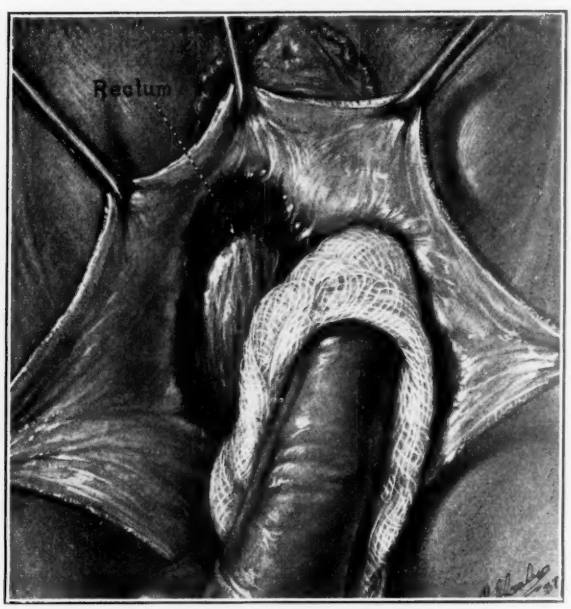

Fig. 10.—Blunt dissection is being used to separate the rectum from the vaginal wall.

taneous traction upon these four clamps clearly defines the triangular area to be denuded of its vaginal mucosa. The simplest procedure is to employ the flap type of dissection with inverted V-shaped resection of the mucosa, extending the apex well above the upper margin of the rectocele. Completion of the denudation exposes the anterior rectal wall, which is freely separated by blunt dissection from the adjacent posterior vaginal wall and pushed back into place. The levator ani muscles together with their overlying fascia are now approximated as one layer by means of three interrupted, buried chromic catgut sutures each one of which is introduced 1 cm. mesial to the skin margin and includes a bite of at least 1.5 cm. in breadth and depth of the fascia and its underlying muscle. The upper one of these sutures is passed as a crown suture according to Emmet's technique. When tied

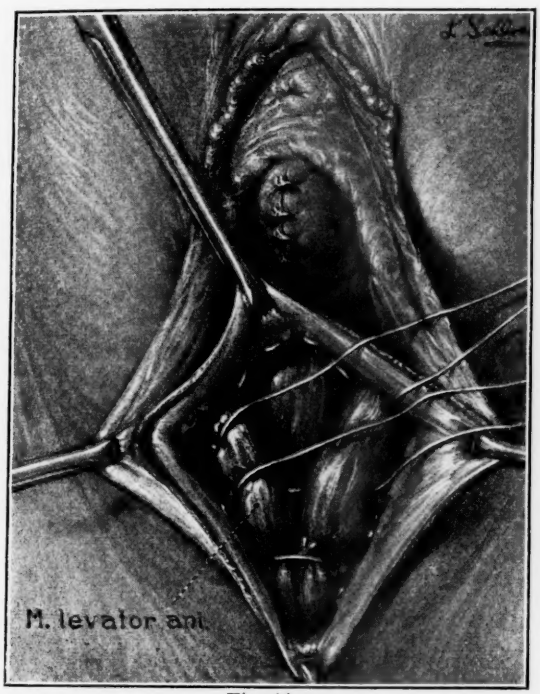

Fig. 11.

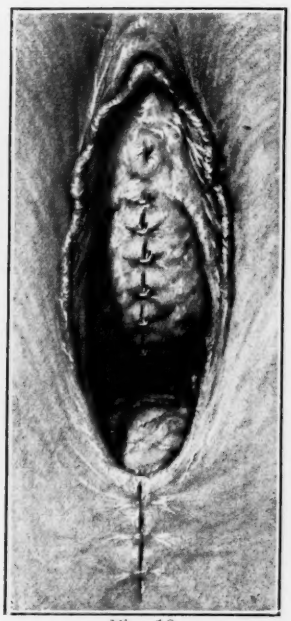

Fig. 12.

Fig. 11.—The levator ani muscles together with their overlying fascia are being approximated as one layer over the rectocele by interrupted sutures of chromic catgut. The redundant flap of vaginal wall has been pared down to proper size.

Fig. 12.—The operation completed with reconstruction of a vagina of normal caliber and depth and restoration of normal anatomical relationships having been achieved.

these sutures reconstruct the pelvic floor, flatten out the posterior vaginal wall, cure the rectocele and narrow the vaginal orifice to any desired extent. The more superficial zone of fascia purposely left between these three sutures and the skin margin when they were introduced is now approximated over them by a continuous suture of plain catgut and the surface wound is closed with a subcutaneous suture of the same material.

If in addition to the rectocele one is confronted also with an enterocele, it is necessary to complete the posterior dissection prior to *Step 7*. An index finger inserted over the cervical stump into the bottom of the culdesac guides the operator in continuing the separation of the rectum from the posterior vaginal wall quite up to

the uterosacral ligaments. The peritoneum of the culdesac is dissected out like a hernia sac, opened, a purse-string suture is introduced about its neck, tied and the sac amputated, after which the uterosacral ligaments are approximated, all according to Ward's technique. The operation is then completed by *Steps 7* and *8*.

COMMENT AND SUMMARY

The admitted incidence of both partial and complete anatomic failure consequent upon utilization of any of the operations commonly employed today in the treatment of advanced grade genital prolapse is undoubtedly responsible for continuation of the search for a more uniformly dependable reconstructive plan, as evidenced by the succession of articles upon this subject to be found in the gynecologic literature of recent years. Inherent defects chargeable to each of the more popular procedures become conspicuously obvious upon a critical comparison of the objective aimed at with that actually attained. Briefly stated, the surgical problem presented by genital prolapse involves: first, complete elimination both of actual and potential disease and, second, restoration with permanent stabilization of normal anatomic relationships. Judged by this standard both colpocleisis and total colpectomy, while possessing undoubted merit, must be regarded as last resort measures which, even if objectively efficient, are both subjectively and anatomically far from ideal. The entire group of transposition operations are open to the objection that they leave the uterus as a potential source of later benign or malignant disease. In total vaginal hysterectomy the most dependable supporting structures are first partly devitalized by the application of crushing clamps, division and ligation with constricting sutures; these same impaired structures are then relied upon to furnish the central and main support of the entire reconstruction plan.

Now the composite operation here offered avoids the objections to the commonly used procedures noted above. By utilization of the time honored high amputation of the cervix coupled with subtotal vaginal hysterectomy, it eliminates existing and potential uterine disease, thereby also relieving the supporting structures of considerable dead weight; by preserving intact that segment of the cervix to which are normally attached the cardinal and the uterosacral ligaments together with the sturdy pubocervical fascia, ideal conditions are created for adaptation of the most dependable features of the several transposition operations; plication of the vesical sphincter is easily executed; accurate identification and dissection of the pubocervical fascia permits imbrication of this valuable unit beneath the bladder neck and urethra in accordance with the established principles of hernioplasty; suture of the round ligaments into the angles of the cervical stump provides additional lift and support; adequate circulation to the cervical stump and attached structures

is assured through preservation of the adjacent main trunks of the uterine vessels and their branches; the ureters are not endangered by any step of the operation; obliteration of the culdesac and plication of the uterosacral ligaments for associated enterocele are readily effected; and, finally, reinforcement of the rectovaginal fascia together with reconstruction of the pelvic floor and perineum completes the operation with accurate restoration of normal anatomical relationships having been achieved. Attention is again called to the fact that every important step of the operation is borrowed from an already well established procedure in the treatment of vaginal herniae. Immediate results in the small series of cases thus far dealt with by this method, totaling about twenty-five, have been completely satisfactory.

9 East Chase Street

PROLAPSE OF THE UTERUS—SHIFTING TRENDS IN TREATMENT*

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AN ANALYSIS of 220 operations for prolapse of the uterus and the end-results obtained by the various operations employed was published in 1928.[1] These operations were performed by the Gynecological Staff of the Michael Reese Hospital and include a number of procedures.

The procedure most frequently employed, the interposition operation, was done in 41 per cent of the series since for many years this operation, when indicated, had proved eminently satisfactory. In the literature current ten years ago vaginal hysterectomy was being advanced as the ideal operative procedure for the average instance of prolapse in women past the child bearing age.[2] With this in mind vaginal hysterectomy spontaneously displaced the interposition operation as the procedure of choice of the Gynecological Staff of the Michael Reese Hospital.

As we stated in the previous communication, the gynecologist, confronted with the problem of curing a patient afflicted with prolapse of the uterus is influenced by three factors in his choice of operation; first, by the limitations and conditions in the given patient; second, by his familiarity and previous success with particular types of operations; and third, by his desire to improve his results through the utilization of other methods.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, Swampscott, Mass., May 31 to June 2, 1937.

A comparable number of operations having been performed since the last series was analyzed (221) it seemed desirable to review the results obtained in both series. This was especially indicated in the light of the more than complete substitution of the interposition operation by vaginal hysterectomy as the operation of first choice.

Coventry and Moe[3] compared the end-results in a similar series of 100 patients. Seventy of the 76 patients on whom the interposition operation was performed were followed and 69 (98.6 per cent) showed successful end-results, there being only one failure. On the other hand, there were 34 treated by vaginal hysterectomy. Twenty-five of the thirty which were followed in this group were successful, five or 16.7 per cent ending in failure.

This series deals with 221 consecutive operations for the relief of prolapse of the uterus as against 220 operations in the previous series. The group of operators remains essentially unchanged. In this series the ages of the patients ranged from twenty-two to seventy-five with an average of 46.2 years. This average is practically identical with our previous series and with the figures given in the literature.

TABLE I. AGE INCIDENCE

		1928 SERIES	1937 SERIES
Youngest 22	Oldest 75	Average 45.8	46.2
Under 30		12	12
30-40		55	60
40-50		80	63
50-60		26	46
60-70		33	33
70 and over		6	7

The women in this series bore a total of 815 children, an average parity of 3.8. The total number and range of parity compares very closely with the previous series.

TABLE II. PARITY INCIDENCE

	1928 SERIES	1937 SERIES		1928 SERIES	1937 SERIES
Nulliparas	5	4	Para viii	9	6
Primiparas	16	18	Para ix	4	7
Para ii	39	48	Para x	5	3
Para iii	44	37	Para xi	2	
Para iv	29	43	Para xii	3	
Para v	25	22	Para xiii	1	
Para vi	21	15	Para xiv	1	1
Para vii	8	9	Average parity	4.2	3.8

Sterilization was done 33 times (14.9 per cent). The disparity in the frequency of this operation in this series with the previous series 102 times (46.8 per cent) is obviously due to the replacement of the interposition operation by vaginal hysterectomy.

TABLE III. STERILIZATION

	1928 SERIES	1937 SERIES
Sterilized	46.0%	14.9%
Sterilized previously	1.3%	
Postmenopausal	40.0%	41.1%

Analysis of Symptoms.—This group showed a considerable increase in two of the outstanding symptoms as compared with the previous series; namely, protrusion and bladder distress.

TABLE IV. SYMPTOMS

	PERCENTAGES IN	
	1928 SERIES	1937 SERIES
Protrusion	58.6	83.7
Discomfort	53.6	46.1
Abdominal pain	18.1	8.1
Backache	28.1	23.1
Bearing down	17.3	14.9
Bladder distress	33.6	40.6
Frequency	30.0	20.8
Dysuria	13.1	10.4
Incontinence	5.4	9.4
Leucorrhea	8.6	14.4
Dysmenorrhea	5.3	1.3
Menorrhagia	7.6	8.5
Metrorrhagia	4.5	9.5

Pathology.—The classification of prolapse commonly accepted and adhered to in the previous publication remains the generally accepted one. First-degree prolapse is defined as a descent of the uterus in which the cervix reaches the level of the ischial spines; second-degree prolapse is a descent of the uterus in which the cervix appears at the vulva; and third-degree prolapse is a protrusion of the cervix or corpus

TABLE V. PATHOLOGY

	PERCENTAGE IN	
	1928 SERIES	1937 SERIES
Prolapse		
First degree	11.4	7.8
Second degree	33.2	35.2
Third degree	55.4	57.0
Cystocele and rectocele	73.6	73.7
Rectocele only	9.5	11.8
Enterocele	1.4	3.1
Fibroids	9.0	17.7
Fibrosis uteri	2.7	2.4
Adenomyosis		5.9
Diseased cervix	24.5	30.7
Polyp	1.3	7.2
	Cases	Cases
Ovarian cyst	5	11
Ovarian fibroid	1	1
Pregnancy		2
Diabetes	6	4
Cardiovascular renal	6	7
Salpingitis	1	1

uteri through the vulva. The objections to this classification are based on the fact that the term "complete prolapse of the uterus" should apply only to those instances in which the entire organ is found beyond the introitus. The classification, however, labels both this condition and protrusion of only the cervix as third-degree prolapse. If the term "procidentia" were reserved for complete prolapse as defined above then the current classification would not be contradictory. We are of the opinion that this classification amplified by the correct use of the term procidentia justifies itself on an anatomic pathologic basis.

It will be noted in Tables I to V given above that enterocele was diagnosed only three times (1.4 per cent) in the series of 1928. In the present series this condition was recognized seven times (3.1 per cent) preoperatively and was discovered subsequent to operation in two additional patients, a total incidence of nine (4.1 per cent). Among the seven patients in whom it was recognized there was one failure following vaginal hysterectomy and repair of the enterocele. This comment was made in the previous article, "If the deep Douglas is a predisposing factor in the development of prolapse of the uterus, the number noted here would seem too small. Either many instances of deep Douglas were overlooked or its significance has been overestimated."

The frequency of this congenital defect, which is regarded as a predisposing factor in the occurrence of enterocele and in the failure of operative cure or prolapse of the uterus has not been accurately determined. Enterocele occurred only nine times (4.1 per cent) in this series.

Previous Operations.—Twenty women in this series of 221 had been operated upon 24 times previously for the cure of their prolapse, one having been operated three times and two twice each. Table VI shows the operations selected in the presence of failure, both in this series and in the series of 1928. It will be noted that vaginal hysterectomy was selected ten times as the method of choice in the presence of a previous failure, whereas in the previous series the interposition operation occupied the leading position. Evidently the operators were definitely in earnest in their determination to evaluate vaginal hysterectomy as a cure for prolapse of the uterus.

TABLE VI

	SERIES 1928	SERIES 1937
Interposition	9	2
Le Fort	6	6
Ries fixation	5	
Ventrofixation	5	
Extrafascial fixation	4	
Ventrosuspension	1	
Vaginal hysterectomy	1	10
Supravaginal hysterectomy		
With stump fixation	1	1
Vaginal plastic		1
Panhysterectomy		1

Operative Procedures.—Table VII shows the frequency with which the various operative procedures were employed in the present series.

TABLE VII. OPERATIVE PROCEDURES

	1928 SERIES	1937 SERIES
Mayo vaginal hysterectomy	7	116
Watkins interposition	91	30
Le Fort vaginal occlusions	14	29
Ventrosuspensions and plastic	14	13
Manchester		9
Ventrofixations and plastic	27	8
Halban-Porges		6
Kocher extrafascial fixations	13	4
Supravaginal hysterectomy and plastic	5	3
Panhysterectomy and Plastic		3
Cervical stump fixations	2	
Kielland-Wertheim interposition	2	
Ries abdominal fixations	28	
Vaginal plastics	17	

Mouth temperatures of 101° F. were considered morbidity in calculating gross morbidity. The value of figures on corrected morbidity is debatable at best. In this paper no attempt has been made to develop figures on corrected morbidity and the comparison with the previous series is shown only in terms of gross morbidity.

Vaginal Hysterectomy.—There were 116 (52.5 per cent) vaginal hysterectomies with one death (0.86 per cent). This occurred in a sixty-three-year-old para v, known to have cardiovascular renal disease with marked hypertension. A vaginal hysterectomy and vaginal occlusion were done under spinal anesthesia. Death occurred on the fifth day due to a postoperative lobar pneumonia. The gross morbidity was 50 per cent. There were fifteen instances of infection of the urinary tract, 5 secondary hemorrhages, and 11 postoperative infections, ranging from stump exudates to two instances of sepsis and one of pelvic peritonitis. Further, there was a postoperative pneumonia, one lung collapse, one bilateral peritonitis and one thrombophlebitis. The remainder (23) was the group of patients with fever and no localization. Sixty-two patients (53.5 per cent) required catheterization more than once. The average hospital stay was 15.3 days.

Interposition Operation.—There were 30 (13.6 per cent) interposition operations. There were no deaths and the gross morbidity was 40 per cent. This included three urinary tract infections, one postoperative hemorrhage, one thrombophlebitis, and one pneumonia. The remainder (six patients) had fever without localization. Thirteen patients (43.3 per cent) required catheterization and the average hospital stay was 13.7 days.

Vaginal Occlusion.—The Le Fort vaginal occlusion operation[4] was done 29 times. There were two deaths in this group. One death was in a seventy-two-year-old, para vi with a known marked cardiovascular

renal disease and coronary sclerosis. The operation was done under local infiltration anesthesia. The patient promptly developed bronchopneumonia and succumbed after twelve days. An ulcerated necrotic adenocarcinoma of the corpus uteri was found at autopsy. There had been no preliminary curettage at the time of operation. The second death occurred in a sixty-six-year-old para ix. This patient was operated upon under ethylene and died suddenly on the sixth day of pulmonary embolism. In the remaining 27 patients there was no morbidity except in one patient who had fever for one day (morbidity 3.7 per cent). Five patients (18.5 per cent) required catheterization and the average hospital stay was 14.4 days.

Ventrosuspension and Vaginal Plastic.—Thirteen patients were operated upon by the Gilliam method of ventrosuspension. A vaginal reconstruction was done in each instance. There was no mortality and the gross morbidity was 7.7 per cent. This is represented by one patient who had a secondary hemorrhage from the plastic operative site. Three patients (23.0 per cent) required catheterization. The average hospital stay was 13.4 days.

Manchester Operation.—There were nine patients operated upon by various modifications of the Manchester procedure[5] with a gross morbidity of 33.3 per cent, which included one instance of sepsis, one instance of pelvic peritonitis, and one of cystopyelitis. Three patients (33.3 per cent) required catheterization and the average hospital stay was 14.8 days.

Vesicofixation.—The Halban-Porges vesicofixation operation[6] was done six times. There were no deaths. Morbidity occurred in three patients (50 per cent) which included one urinary tract infection and two instances of fever. Three patients (50 per cent) required catheterization and the average hospital stay was 16.8 days.

Extrafascial Fixation.—The Kocher extrafascial abdominal fixation[7] was done four times. There were no deaths. There was a morbidity of 25 per cent due to one wound infection. Catheterization was necessary in one patient (25 per cent). The average hospital stay was 15.2 days.

Ventrofixation and Vaginal Plastic.—Eight patients were operated upon by ventrofixation of the uterus and vaginal plastic. There was no mortality and the gross morbidity was 12.5 per cent due to the development of sepsis, peritonitis, and a jejunal fistula in one patient. Following recovery from the infection, this fistula was repaired with good results. Two patients (25 per cent) required catheterization and the average hospital stay was 24.1 days.

Supravaginal Hysterectomy.—Three patients were treated by supravaginal hysterectomy and vaginal plastic. There were no deaths. Morbidity included one patient who had fever for several days, one patient required catheterization and the average hospital stay was fifteen days.

Panhysterectomy.—Three patients were treated by panhysterectomy. There were no deaths. All three patients had fever (100 per cent), one of these developing a vesicovaginal fistula and one a wound infection. One patient required catheterization and the average hospital stay was 31.3 days.

TABLE VIII. OPERATIVE RESULTS

OPERATIONS	1928 SERIES			1937 SERIES		
	NO.	DEATHS	GROSS MORBIDITY PER CENT	NO.	DEATHS	GROSS MORBIDITY PER CENT
Interposition	91	1	55.1	30		40.0
Vaginal hysterectomy	7	1	43.0	116	1	50.0
Ries fixation	28	1	35.7			
Ventrofixation and plastic	27		44.4	8		12.5
Vaginal plastic	17		11.8	9		33.3
Vaginal occlusion	14		21.7	29	2	3.7
Ventrosuspension	14		57.1	13		7.5
Extrafascial fixation	13		46.0	4		25.0
Supravaginal hysterectomy and plastic	5		60.0	3		33.3
Cervical stump fixation	2					
Panhysterectomy and plastic				3		100.0
Kielland-Wertheim interposition	2	1				
Halban-Porges				6		50.0
Total and average	220	4 (1.8%)	44.5	221	3 (1.3%)	37.7

REMOTE RESULTS

The end-results in this series were determined by examination made either by the operator or by some other member of the department, as in the previous series. The obtainable records of those women who were reexamined from four months to seven years postoperative supply the data for the analysis of remote results. Criticism of conclusions as to remote results in less than two years after operation is justifiable. Still it is undoubtedly true that the vast majority of failures is seen promptly after operation. Since the same period of observation was used in the previous series, it was again utilized here to afford us a basis of comparison.

There were three deaths among the 221 patients (1.3 per cent). Remote results were obtained in 127 patients (57.4 per cent). One hundred (78.7 per cent) were successful, 18 (14.2 per cent) were partially successful, and 9 (7.0 per cent) were failures. The operative end-result, as with the previous series, was considered only partially successful, if a third-degree prolapse recurred as a first-degree prolapse or if a cystocele or rectocele recurred. Combining the improved and cured groups, 118 (92.9 per cent) were successful.

Vaginal Hysterectomy.—This operation practically replaced the interposition operation. Sixty-five patients were followed, and among

these 46 (70.7 per cent) presented successful end-results. Twelve (18.4 per cent) were partially successful. Seven (10.8 per cent) had a prolapse of the vagina and were classified as failures.

Interposition Operation.—In 19 patients in whom the interposition operation was done, the outcome was completely successful in 17 (89.5 per cent); there were two partial successes (10.5 per cent) and no failures.

Le Fort Vaginal Occlusion Operation.—End-results were obtained in 18 women. Of these, 17 (94.4 per cent) were successful and there was one (5.6 per cent) failure.

TABLE IX. FOLLOW-UP RESULTS

OPERATION	NO. FOLLOWED	1928 SERIES			NO. FOLLOWED	1937 SERIES		
		SUCCESS	PARTIAL	FAILURE		SUCCESS	PARTIAL	FAILURE
Entire series	121	85.8	6.1	8.1	127	78.7	14.2	7.1
Interposition	64	87.5	4.7	7.8	19	89.2	10.8	
Vaginal hysterectomy	5	100.0			65	70.7	18.4	10.9
Vaginal occlusion	10	100.0			18	94.4		5.6
Ventrosuspension	11	91.0		9.0	6	66.6	33.4	
Ventrofixation	19	94.7		5.3	4	75.0	25.0	
Kocher	12	100.0			4	75.0		25.0

CHOICE OF OPERATION

The interposition operation was completely successful in 56 out of 64 (87.5 per cent) in the series previously published. In the present series, the interposition operation was successful in 17 out of 19 (89.5 per cent). Vaginal hysterectomy, to which we turned in order to improve our results and the results of which were followed in 65 women, was successful in only 46 instances (70.7 per cent). The patients in both series were operated upon by the same group of gynecologists. Since it may be assumed that these operators were equally competent in both types of operation, the results obtained emphasize the superiority of the interposition operation over vaginal hysterectomy in our hands.

In the light of this outcome it seems appropriate to quote from the 1928 report as follows:

"The value of the Mayo vaginal hysterectomy for the cure of prolapse of the uterus cannot be discussed further than to point out that preservation of the uterus and its utilization has seemed fundamental to the gynecological department of the Michael Reese Hospital. The results presented here apparently justify a continuation of those types of operation in use at present."

It is our intention to again avail ourselves of the interposition operation as a cure for prolapse of the uterus wherever the conditions for its selection are met. To quote from the previous report "it is selected for those patients with a large cystocele, a corpus uteri neither too large

nor too small, freely movable and without gross adnexal pathology."

Vaginal hysterectomy will be restricted to those instances of prolapse in which the pathology of the uterus itself carries the indication for hysterectomy. The Le Fort vaginal occlusion operation should retain its value for older women with atrophy of the cervix and with senile atony of the anterior and posterior fascial and muscular structures and in whom marital relations have terminated.

In women with prolapse in whom childbearing is to be conserved, we have heretofore recommended ventrosuspension combined with a vaginal reconstruction. We still maintain this position in regard to third-degree prolapse. Both the Manchester operation and the Halban-Porges vesicofixation are superior in first and second-degree prolapse. We have not determined to our satisfaction which of these various methods is best suited for the cure of prolapse plus conservation of childbearing.

SUMMARY

In 221 operations for prolapse of the uterus, the average age was 46.2 years and the average parity was 3.8. Ninety-one patients (41.1 per cent) were in the menopause and 33 patients (14.9 per cent) were sterilized. Seventeen patients (7.8 per cent) had a first-degree prolapse, 76 (35.2 per cent) had a second-degree prolapse, and 123 (57 per cent) had a third-degree prolapse. Ten types of operations were employed. Based on the immediate and remote results, three of these are well suited to meet particular indications; namely, the Watkins interposition operation, the Le Fort vaginal occlusion operation, and the Mayo vaginal hysterectomy. We believe the interposition operation should take precedence over vaginal hysterectomy wherever the conditions for its selection are met. Vaginal hysterectomy should be restricted to prolapse in which the pathology of the uterus itself carries the indication for hysterectomy.

The Le Fort vaginal occlusion operation is indicated for older women with atrophic genitalia in whom marital relations have terminated. For the childbearing group the choice lies between the Manchester operation and the Halban-Porges operation for first- and second-degree prolapse. The Gilliam suspension operation, combined with vaginal reconstruction is best suited for third degree prolapse.

There were three deaths (1.3 per cent). One was from lobar pneumonia, one from bronchopneumonia, and one from pulmonary embolism.

End-results by personal examination were obtained after 127 operations (57.4 per cent). Of these 100 (78.7 per cent) were successful, 18 (14.2 per cent) were partially successful, and 9 (7.1 per cent) were failures. Combining the cured and improved groups, 118 (92.9 per cent) were successful.

Acknowledgment is hereby made to the members of the Gynecological Staff of the Michael Reese Hospital for the use of their records.

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104 South Michigan Avenue

DISCUSSION ON PAPERS BY DR. JOSEPH L. BAER AND DR. EDWARD H. RICHARDSON

DR. THOMAS C. PEIGHTAL, New York, N. Y. (By Invitation).—Our attack upon the problem of prolapse has received new impetus in recent years from a better anatomic knowledge of the true supporting structures of the uterus and vagina. This knowledge has served as a stimulus to devise new operative procedures, but, for the most part, it has been responsible for reviving and popularizing certain older principles of technic not commonly used in the average clinic. For the same reason on many services there is at present a desire to appraise the end-results of previous methods and to re-plan an operative attack based upon both past experience and this newer knowledge.

The two papers under discussion do exactly this. Dr. Richardson, having found figures which favor the interposition operation over total vaginal hysterectomy, has used this experience in devising a composite operative procedure which is carefully designed to meet all the complex problems of extensive uterine prolapse and vaginal hernias in elderly women. The interposition principle is emphasized, the parametrial fixation feature is introduced, and the value of removing the pathologic portions of the uterus when indicated, is not lost. Cystocele, rectocele, enterocele, and relaxed urethral sphincter also are corrected. The retention of at least an outer cuff of the upper portion of the cervix provides the keystone, so to speak, upon which the interposition and parametrial fixation principles of this procedure are built. Some may level criticism at the retention of this portion of the cervix, but, as Dr. Richardson uses it, there is no doubt that he not only avoids devitalization of its ligaments but that he secures a firmer attachment of them. The other features of the operation are all well proved principles upon which there can be no controversy.

In Dr. Baer's paper the chief interest lies in his estimate of the comparative effectiveness of the Watkins interposition operation and the Mayo vaginal hysterectomy. The fact that these two series have come from the same group of operators has eliminated many of the variable factors which confuse the usual statistical studies.

In order to formulate better our own conclusions concerning remote results in the operative treatment of prolapse, we have analyzed briefly 111 followed cases over the five-year period up to January 1, 1936, at the Roosevelt Hospital. Of this group, one-fifth had complete prolapse (procidentia) while four-fifths had varying degrees of partial prolapse. In the procidentia group interposition operation was done twice as often as vaginal hysterectomy, but vaginal hysterectomy gave more successful results. In the partial prolapse group there were mainly three operations: one-half were treated by a vaginal plastic combined with ventrosuspension or fixation; one-third by the interposition operation, because of the degree of the cystocele; and one-sixth by vaginal hysterectomy, mainly because of the amount of the descensus. In this partial prolapse group, the interposition operation was just as superior to the other procedures as Dr. Baer has indicated in his paper. Late

results of the total group, graded after the manner used by Dr. Baer, show figures almost identical to his, 77 per cent successful, 16 per cent partially successful, and 7 per cent failures.

Over the five years the incidence of the various operations used indicates a definite trend. In procidentia, there is a tendency to use vaginal hysterectomy more often and interposition less often. In partial prolapse the trend is to use plastic repair plus ventrosuspension if the cystocele is of moderate degree, interposition operation if the cystocele is large and with not too much uterine descensus, while vaginal hysterectomy is reserved for those cases where descensus is the main factor. Ventrofixation, formerly practiced, has not been done in three years.

DR. WALTER T. DANNREUTHER, NEW YORK, N. Y.—Vaginal hysterectomy, interposition of the uterus, and the Manchester operation are probably the most popular reconstructive methods at the present time, and I believe that most of us have been satisfied with the end-results. Bullard has reported 95 per cent cures after vaginal plastic surgery in 461 cases done by 30 different operators, which is not far from Dr. Baer's report of 92.2 per cent successes. The 4 per cent incidence of failure after the interposition operation, reported by Dr. Richardson, is not at all high, but 30 per cent of failures after vaginal hysterectomy is not only discouraging but astonishing.

Dr. Baer's presentation indicates that the trend at the Michael Reese Hospital is now back toward the interposition operation. This is apparently due to the fact that vaginal hysterectomy has been followed by an incidence of 10.8 per cent failures, contrasted with none after the interposition operation. This discrepancy would be more significant if the statistics represented the work of a single operator.

It is difficult to agree with Dr. Baer's assumption that all of "these operators were equally competent in both types of operation." Even if this were true, there would still be variation in the selection of cases, differences in surgical judgment, and modifications of technical details, all of which have a direct influence on the end-results. It would be interesting to know how closely Dr. Baer's personal results correspond with the figures furnished by the group of operators.

The interposition operation is absolutely contraindicated before the menopause. Pregnancy, fibroids, and carcinoma in a transposed uterus are serious therapeutic problems. A diagnostic curettage should precede an interposition operation without exception.

DR. JAMES C. MASSON, ROCHESTER, MINN.—There is a legitimate field for both the Mayo type of vaginal hysterectomy and the Watkins-Wertheim interposition operation. The interposition operation gives the best results in cases in which there is a marked cystocele but a prolapse of not more than the second degree. On the other hand, a vaginal hysterectomy is indicated in patients with large cystocele and also marked prolapse of the uterus.

To extend the field of usefulness of the interposition operation, I frequently reduce the size of the uterus in women close to the menopause age by excising the greater part of the anterior wall, all the endometrium, and all the cervix. It is a rather bloody operation, but I feel that it is preferable to doing a subtotal hysterectomy and leaving the cervix, which is more likely to give trouble than any other part of the uterus. By this operation we effectively sterilize the patient, reduce the danger of any tumors developing in the uterus and in a large measure protect against leucorrhea.

DR. GEORGE GRAY WARD, NEW YORK, N. Y.—Dr. Richardson stresses the complexity of the surgical problem and states that there is not a single plan of reconstructive surgery yet devised that is applicable to all types. I am heartily in

accord with this statement, and believe it is the whole gist of the matter. The judgment of the surgeon in selecting the type of operation for each case determines the ultimate result.

In cases where it is advisable to conserve the uterus, I believe that the cure of prolapse should be accomplished by utilizing the principal support of this organ, namely the cardinal ligaments, reefing them by approximation in front of the cervix, or shortening them by the interposition operation.

We hear much about the Manchester operation today. It is correct in principle because it utilizes the normal supports of the uterus. Donald used this technic in 1888, but it was not until Fothergill perfected and published the operation in 1907 that it became popular. In his paper he gives credit to Alexandroff in 1903 and Tweedy of Dublin in 1905 for publishing their technic and stressing the importance of using the paracervical tissues to give the necessary support.

These slides I show, which were taken from the original illustrations, prove that great minds have thought in the same channels for many years past. Emmet in 1869 utilized the same principle. He denuded the vaginal fornix on each side of the cervix at the base of the broad ligament and an area anterior to the cervix. He brought these three points together with silver wire, thus approximating the base of the broad ligaments in front of the cervix. In 1912 Baldwin of Brooklyn improved this technic and reported excellent results. Alexandroff in 1903 placed a suture in each cardinal ligament and crossed them, and then sutured the ligaments together in front of the cervix. Again we see the same principle employed by Tweedy in 1895. E. C. Dudley of Chicago in 1906 published his operation where he cut the cardinal ligaments from the cervix and sutured them together and to the front of the cervix. Hertzler of Kansas in 1906 published the same technic but overlapped the ligaments. He stated he had been doing it with success for four years. Nyulasy of Australia in 1908 accomplished the same result but from above. Halban's technic in 1919 has the same principle.

In the nonchildbearing age, where there is uterine pathology present, the Mayo type of operation gives excellent results, provided an enterocele is eliminated or prevented by dissecting out the peritoneal pouch of Douglas and uniting the uterosacral ligaments. In 116 cases of this type I found 83 per cent had some pathologic condition of the uterus which made removal of the organ desirable.

DR. HERMAN J. BOLDT, WHITE PLAINS, N. Y.—Where sexual relations have ceased, in elderly women, and where there is complete procidentia of the uterus and vagina, I have not found any form of operation that will equal the complete extirpation of both uterus and vagina. This is an operation that was devised many years ago by Dr. Edebohls. I have done it whenever it was indicated. It is done much more rapidly than any other operation; there is no more morbidity and it brings an absolutely perfect cure.

DR. LILIAN K. P. FARRAR, NEW YORK, N. Y.—There is one point in technic I would like to mention. When in performing a vaginal hysterectomy for prolapse of the uterus and either the broad ligaments or the cervix are fastened forward, the intraabdominal pressure will then fall on the stretched-out uterosacral ligaments and an enterocele is almost sure to develop. It is a simple matter to unite the uterosacral ligaments and prevent this occurrence. I believe that utilizing the cervix as Dr. Richardson has described is a valuable procedure.

Several years ago Dr. Howard A. Kelly brought to me a patient who had had a supravaginal hysterectomy done twenty years before, and who then had a prolapse of the cervix and a large cystocele. I decided to split the cervix and dissect off the mucous membrane and vaginal mucosa, suture the stump to the pubis and sew the fascia below as in a Watkins operation. The result was absolutely satisfactory,

and I have followed this procedure in similar cases since, so I am glad to endorse heartily the technic Dr. Richardson has presented.

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—Two hundred and three vaginal hysterectomies have been carried out in the past few years on our service. Eighty were done for a descensus of greater or less degree. In this group we had three distinctly poor results, and two or three others which were unsatisfactory. These poor results are due particularly to failure to adopt a precaution which Dr. Farrar has mentioned, that is, the uniting of the uterosacral ligaments.

DR. BAER (closing).—Dr. Peightal drew exactly the right conclusion, that we are limiting the place of vaginal hysterectomy and shifting back to the interposition operation. We are now much interested in the Manchester operation. The operation has, however, a limited place in women of the childbearing age, with complete prolapse. We believe the Gilliam ventrosuspension is the procedure of choice for complete prolapse, and the Manchester is better for partial prolapse.

Dr. Dannreuther's comment was entirely pertinent. The single series results perhaps lend themselves better to conclusions than group series, and yet we believe that the group in which I work is a fairly well-coordinated group and so we feel justified in presenting a summation of our results and a comparison of the two series. My personal results closely parallel those of the group.

Of course, pregnancy, carcinoma, and fibroids may develop in the interposed uterus. The incidence is fortunately very, very low. And if the interposition operation has the merit which most of you seem to believe it has when properly selected, I still think it should be chosen plus sterilization even in the menstruating woman, regardless of the possibility of the three types of pathology developing in such an interposed uterus.

The technic of the interposition operation must be properly carried out, as in all others; the patient must be well selected, and the result then is satisfactory. I am particularly glad that the Society accepted this rebirth of the interposition operation, because I think it was being slowly shelved, and I am glad to have had some small part in recalling it to your attention.

The mutilation of the uterus which Dr. Masson indicated is desirable in some instances of interposition, but this procedure which he himself characterized as a bloody operation, might perhaps be replaced by what Dr. Richardson suggests in his paper, the modified interposition plus the Manchester characteristics.

AN UNUSUAL OBSTETRIC INJURY CAUSING DETACHMENT OF BLADDER AND URETHRA FROM THE SYMPHYSIS PUBIS AND COMPLETE EPISPADIAS*

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THE following case report seems worthy of publication because of the unusual character and extent of the obstetric injury, and because of the problems encountered in attempting to restore the patient's control of her bladder function.

Mrs. B. M., aged thirty-eight years, at term with her first pregnancy, entered the Church Home and Infirmary on Aug. 28, 1935. The fetal head was engaged in the L.O.A. position and labor progressed very slowly with alternate recessions until, at the end of sixty-six hours, the cervix seemed fully dilated and the membranes ruptured. The second stage took one hour and twenty minutes and ended with the precipitate expulsion of a normal male child weighing 8 pounds and 5 ounces. It was apparent that the patient had received extensive lacerations and Dr. Gerald Ackerman, the assistant resident surgeon, was called and on his arrival the third stage of labor had ended normally. The patient was placed under light general anesthesia.

Examination revealed an inverted T laceration extending from the clitoris downward, exposing the deep fascia over the lower portion of the symphysis pubis. The tissues of the vestibule had been swept away. The external urethra at first could not be located. The laceration extended to the anterior cervix where it branched laterally to form the inverted T, suggesting the preliminary incision for an interposition operation. Both triangular flaps of the anterior vaginal wall had been denuded from the underlying tissues of the base and posterior walls of the bladder, and these bladder walls now protruded as a large cystocele. On further search for the urethra, pressure over the cystocele caused a free gush of urine from an opening situated several centimeters back of the symphysis pubis. It was then found that the entire anterior wall of the bladder together with the urethra had been torn from their attachments in the symphysis region. The anterior wall of the urethra had been laid wide open (Fig. 1), and the tear had extended through the muscles of the internal sphincter and for a short distance up the anterior wall of the bladder.

In his repair work Dr. Ackerman placed a mushroom catheter in the bladder and, using interrupted sutures of twenty-day chromic catgut, began at the upper end and brought together in succession the torn edges of the bladder, the internal sphincter region, and the anterior wall of the urethra. He then attempted with the same suture material to get anchorage in the periosteum of the region of the pubic arch and draw the prolapsed tissues forward beneath the symphysis. Finally, the posterior walls of the bladder forming the cystocele were covered with the denuded vaginal flaps by interrupted sutures which completed the approximation of the inverted T laceration.

*Read at the Sixty-second Annual Meeting of the American Gynecological Society, at Swampscott, Mass., May 31 to June 2, 1937.

I was asked to examine the patient on September 19, twenty days after the accident. For the previous week there had been partial continence, especially when the patient was lying flat in bed, the voidings amounting to about 200 c.c., but as soon as she assumed the erect posture there had been continuous leakage.

Fig. 1.—Sagittal view illustrating separation of bladder and urethra from pubic attachments. *A*, Retracted dorsal wall of complete epispadias. *B*, Opening into bladder. *S*, Retracted fibres of internal sphincter.

On examination with the patient in the lithotomy position, the outlet was fairly well lifted, and the introitus admitted two fingers easily. The levator muscles seemed well preserved. There was only a moderate degree of cystocele and rectocele. The cervix was somewhat prolapsed, but pointed about normally posteriorly. The fundus, in about normal involution, was sagging to some extent and occupied a position back of the normal axis.

The immediate repair of the inverted T laceration had healed satisfactorily over the portion involving the genital tract, but as regarded the urinary passages all the

repair work had given way except possibly in the anterior wall of the bladder where healing had taken place down to but not including the internal sphincter.

The tissues of the anterior wall of the bladder and of the urethral region had again prolapsed backward away from the symphysis region, and the anterior wall of the urethra including the internal sphincter region lay wide open.

Immediately beneath the symphysis there was a diamond-shaped opening measuring about 2 cm. on each of its 4 sides. Its anterior legs met at the symphysis joint and were composed of the inferior edges of the pubic rami denuded of all tissues down to the periosteum. The posterior borders of the diamond-shaped opening met at the external orifice of the urethra and were composed of the widely gaping tissues about the external orifice, and by the prolapsed tissues of the vestibule region of the anterior vaginal wall, which probably contained torn fragments of the ischiocavernosus, bulbocavernosus and deep transversus perinei muscles. The anteroposterior measurement of the diamond-shaped opening from the symphysis to the external urethra was about 2.5 cm. With reflected light from the head mirror one could look through this opening into the space of Retzius which, with the detachment and prolapse of the anterior wall of the bladder, had become enormously enlarged (Fig. 1). This space was roughly triangular or pyramidal in form, its base being formed by the prolapsed anterior wall of the bladder, its anterior boundary by the pubic rami, and its posterior face by the loosened peritoneum. A uterine sound, laid horizontally along the anterior wall of the bladder until its tip was stopped by the peritoneum, entered the cavity for a distance of from 6 to 7 cm. beyond the symphysis. The anterior (bony) wall and the posterior (peritoneal) wall of the space of Retzius were apparently of about the same dimensions as the base. This base, or floor of the space of Retzius, formed by the anterior wall of the bladder was paved with apparently healthy, bright red granulation tissue. The condition of epispadias involving the entire urethra exposed the red urethral mucosa of the posterior and lateral walls, and the internal sphincter region opened rather widely into the bladder. The index finger entered the bladder to the first joint, and with thumb and finger the retracted bundle of sphincter muscles could be palpated posteriorly. Anteriorly, palpation with thumb and finger showed considerable thickening of the anterior bladder wall next to the sphincter region, probably due to its recent repair together with the heavy layer of granulation tissue covering the entire anterior wall.

It was manifest that reconstruction of the urethra ought not be attempted until nature had been given time for such repair work as could take place. Accordingly, the patient was dismissed from the hospital, with instructions to return for observation at about monthly intervals.

The subsequent course of events can probably be made clear by quoting from our history records:

Oct. 15, 1935. Since returning home the patient has gained in strength and now looks well. The urine is retained perfectly for about two hours while she is lying down, but while on her feet she has no control. On examination the external urethra, the lateral walls of the urethra, and the entrance to the bladder appear about as formerly; but the large triangular area back of the symphysis, representing the space of Retzius, and formerly measuring about 6 or 7 cm. across each of its 3 walls, is now completely closed. Red granulation tissue overhangs the internal sphincter region, and on the right of the bladder opening there is a large protruding nodule of granulations.

Jan. 10, 1936. Patient looks well and says she is feeling well except for the incontinence. There is a moderate degree of cystocele and rectocele. The red, granulation masses seen in October as the final process in the filling in of the space of Retzius have now entirely disappeared and the infrapubic tissues are covered with epithelium,

the portion which lines the epispadic urethra presenting a deep red color. The urethra has been drawn forward to a position somewhat nearer the symphysis. The large lateral labia of the external urethra show the orifices of the ducts of Skene's glands (Fig. 2). With the index finger in the bladder opening, one can outline on the floor of the sphincter region a large crescentic bundle of tissue probably representing the retracted sphincter muscles, but on asking the patient to contract these muscles no evidence of contraction can be felt.

Nature had solved our first problem, that of filling up the space of Retzius and drawing the bladder forward to its old position back of the pubic bones. Our second problem was concerned with the reconstruction of the urethral channel, and we decided to wait another month for further repair of the infiltrated tissues.

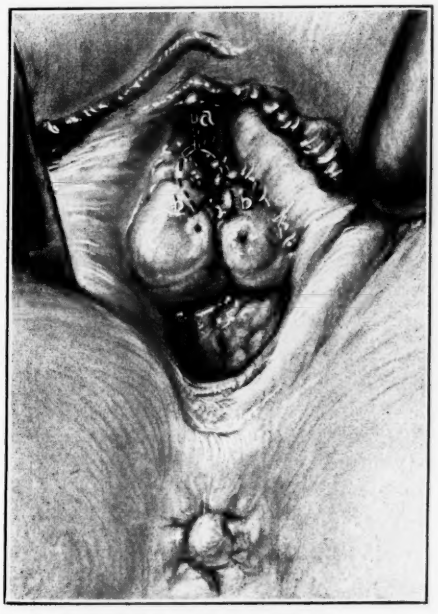

Fig. 2.—Incision for second operation, the reconstruction of the epispadic urethra.

Feb. 8, 1936. Patient readmitted yesterday, five months after her injury. While in the recumbent position, lying on her back or on either side, she is able to retain her urine for two or even three hours, but complete incontinence persists while she is on her feet.

Operation under avertin anesthesia supplemented with nitrous oxide gas. Repair of complete epispadias. A No. 9 male rubber catheter was inserted into the bladder and allowed to rest in the trough formed by the posterior and lateral walls of the urethra. An incision was made beneath the symphysis pubis, beginning in the midline next to the periosteum (Fig. 2, *a*). After carrying this downward about 15 mm. we met the upper edge of what was virtually a vesico-urethrovaginal fistula. The incision was then divided and carried down the outer edge of the urethral mucosa on either side (Fig. 2, *b*). The urethral mucosa was then carefully dissected away from the vaginal mucosa on both sides. With a continuous Lembert suture of No. 2 plain catgut, we began at the upper end and brought together, back to back, the two edges of urethral mucosa down to the external orifice. After the Lembert suture, to restore

the dorsal wall of the urethra, we attempted to pick up the ends of the internal sphincter muscle and bring them together across the dorsum, but all the tissues in the region of the sphincter ends were so infiltrated that we could not make a satisfactory suturing from side to side. We found that the tissues beside the urethra were more pliable and could be brought up over the sphincter region with sutures introduced up and down. Three No. 00, forty-day catguts were set in the vertical direction, and these reinforced with fresh tissues both the unsatisfactory sphincter closure, and the Lembert line along the dorsum of the urethra. After this further similar catgut sutures were taken in any direction that promised the filling in of prospective dead spaces.

Finally, the vaginal mucosa was brought together from side to side with interrupted black silk sutures. Because of the dearth of plastic vaginal mucosa in the vestibule, after all this region had been swept away from the symphysis, we were able to close the vaginal mucosa across only the lower half of the urethral tube. This left to be closed in by granulation a considerable triangular area measuring about 2 cm. on each of its three borders and lying over the internal sphincter region. However, as above described, we had been able to cover this sphincter area with a considerable amount of fresh tissue from beside the urethra, and it appeared that successful granulation might be expected before any tension would disrupt the sutures.

The small male urethral catheter was strapped to the inner thigh, and orders were given to irrigate the bladder twice daily with 200 c.c. of 1:1,000 silver nitrate solution and at the same time to flush the granulating area with about 100 c.c.

On the sixth day after operation the rubber drainage catheter came out and by the time the resident surgeon could arrive from the operating room to replace the catheter, 300 c.c. of urine had accumulated in the bladder without leakage.

On the twelfth day after operation some of the black silk sutures and on the seventeenth day the remaining stitches were removed. The vaginal flaps over the lower urethra had separated slightly in places because of tension, but the bared areas showed apparently healthy granulations, as did the large triangular area over the upper half of the urethra. The catheter was removed and instructions were given to put a commode beside the bed for use if the patient found that she could void more easily in the sitting posture than by using the urinal in bed.

In the hope of developing the remaining fibers of the internal sphincter muscle a course of treatments was instituted, in which the faradic electric current was applied for ten minutes each day over the sphincter region. This treatment was continued after she went home on March 1.

March 25, 1936. The patient says she is improving slightly but steadily. She has taken the electrical treatment daily except during four days of menstruation. She can control the urine at night for from four to five hours, and then awakens and voids without preliminary leakage. During the day, when she is about on her feet, she has practically no control. Occasionally she has a desire to void but never can pass more than one ounce. *Cystoscopy:* Knee-chest posture. Urethra takes Nos. 7, 8, and 9 Hegar dilators with a slight resistance to each. The Kelly speculum No. 8, when introduced, meets with definite obstruction as it goes through the internal sphincter region. The bladder mucosa appears normal. On withdrawal of the speculum the tissues of the internal sphincter region close about its end in a sluggish way as if the sphincter exerted no action. The urethra seems to be slightly longer than normal, measuring between 3 and 4 cm. The patient was advised to continue the electrical treatment daily for another month.

Oct. 23, 1936. The patient says she is leaking about as badly as ever. If she lies quietly on her back or side, it takes about three to four hours for the bladder to get full, but when she gets up to void, she leaks as soon as she assumes the erect posture. *Examination:* On separation of the labia the external orifice of the urethra

was still found to sag posteriorly at a distance of about 2 cm. from the arch of the symphysis (Fig. 3). We decided to see whether elevating the external urethra and bracing it up in a more normal position against the symphysis might improve the degree of continence.

Third operation: On October 26 the patient was given by rectum a small dose of avertin and this was supplemented with nitrous oxide anesthesia. A diamond-shaped area of tissue was laid bare, each side measuring about 15 mm. With a small staphylorrhaphy needle and No. 32 virgin silver wire, the mucosa in the upper

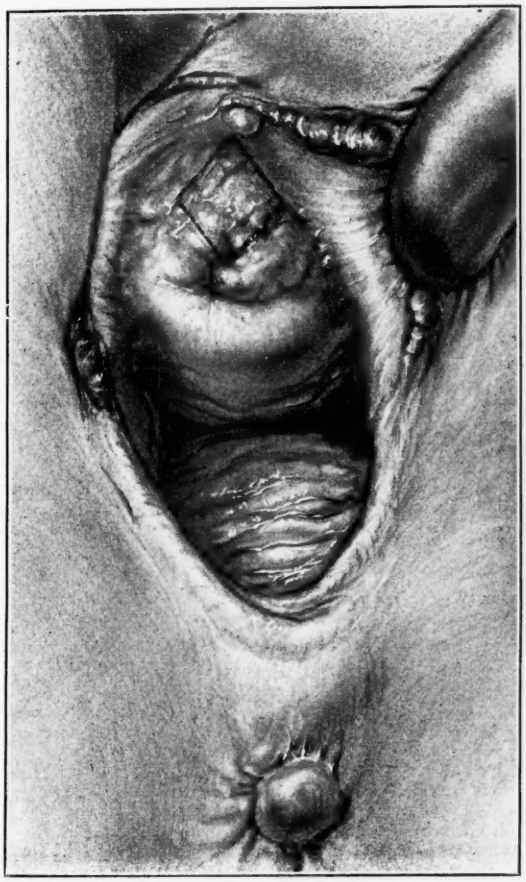

Fig. 3.—Incision for third operation, an attempt to draw the external half of the urethra closer to the symphysis.

edge of the external urethral orifice was transfixed, carried to the upper angle of the bared area, and the suture set through the periosteum and mucosa beneath the symphysis. The lateral edges were brought together with sutures of fine black silk. A No. 10 male rubber catheter was kept in the bladder for three days after which it was removed and the patient allowed to use a commode.

By the end of the eighth day the silver wire and some of the black silk sutures had cut through, but the healing had been fairly satisfactory. However, the external orifice had not been permanently drawn forward for more than half the distance we had anticipated, and the final result had not appreciably improved the patient's control of her bladder.

From the nature of the urethral injury which had completely severed all the fibers of the internal sphincter region, allowing them to retract to the inferior arc of the sphincter circle, it was probable that no form of puckering or shortening of

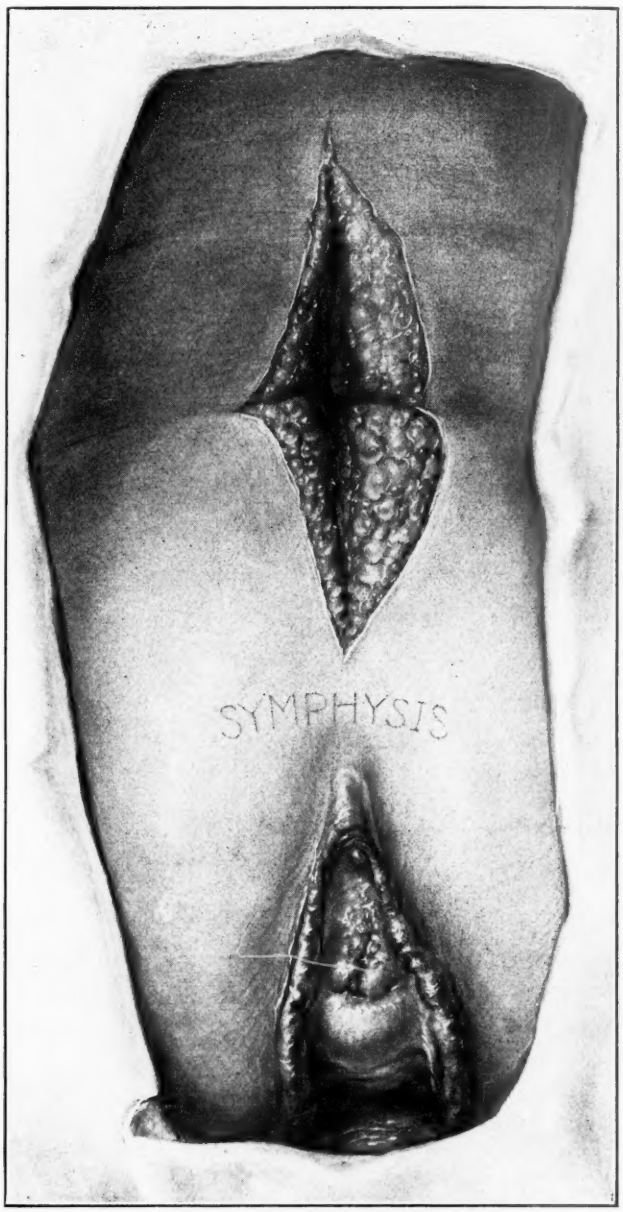

Fig. 4.—Illustrating draping of patient preliminary to the fourth and final operation.

these muscles by a suburethral aproach would have restored their function. Success was rendered more unlikely because of the probable destruction of the chief nerve supplies to all portions of the urethra, the original injury manifestly having destroyed

much of the involuntary internal sphincter or trigonalis muscle, and much of the voluntary muscles, with their nerves, derived from the urogenital diaphragm and the bulbocavernosus.

This situation seemed to call for a transplantation of muscle, and the most promising method appeared to be the Miller[1] modification of the Goebell-Stoeckel pyramidoplasty.

Fourth operation: Jan. 10, 1937. *Avertin, gas and ether anesthesia. Restoration of urethral control by modified Miller-Stoeckel pyramidoplasty, cure of cystocele by interposition operation, cure of rectocele by plastic repair of levator ani muscles.*

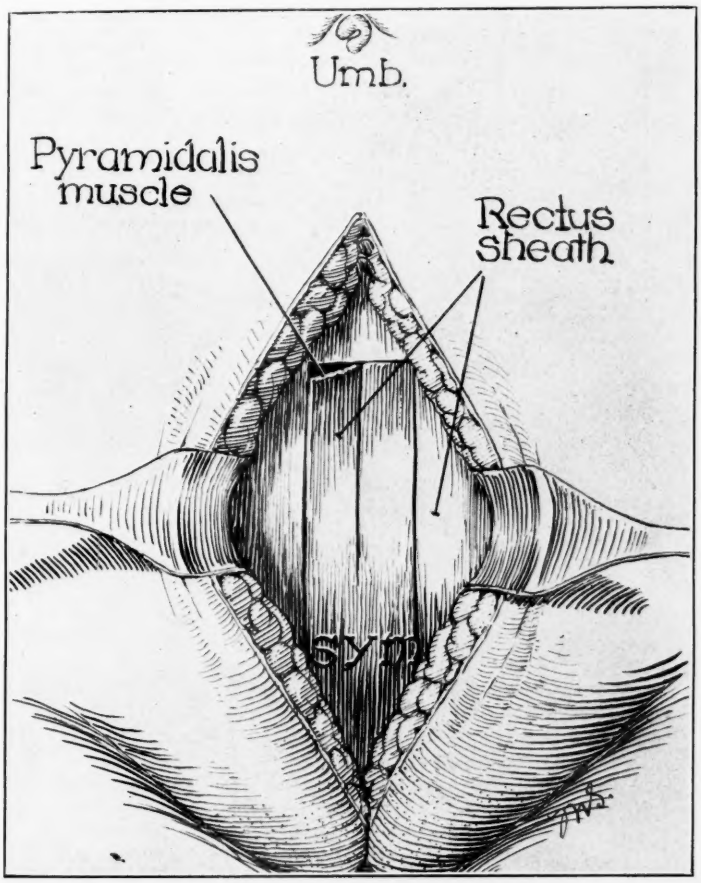

Fig. 5.—The strip of fascia with subadjacent pyramidalis muscle is cut and divided longitudinally.

The patient was placed in a modified lithotomy position and draped so that the entire operation could be done without change of position on the table. A midline incision was made, extending for two-thirds of the distance between the symphysis and navel (Fig. 4). Blunt dissection of the fat in the anterior wall from the deep fascia over the rectus muscles. At a point about one-third the distance below the navel we made a small transverse incision across the midline, this incision through the fascia of the rectus being almost 2 cm. long (Fig. 5). A vertical incision was carried from each end of this transverse incision down to a point about 1 cm. from the symphysis. We then lifted this entire flap from the rectus muscles, beginning

above and carefully dissecting the flap downward to the region of the symphysis. This flap contained a small bundle of fibers from the median edge of each rectus muscle. When we reached the upper ends of the pyramidalis muscles, we carefully

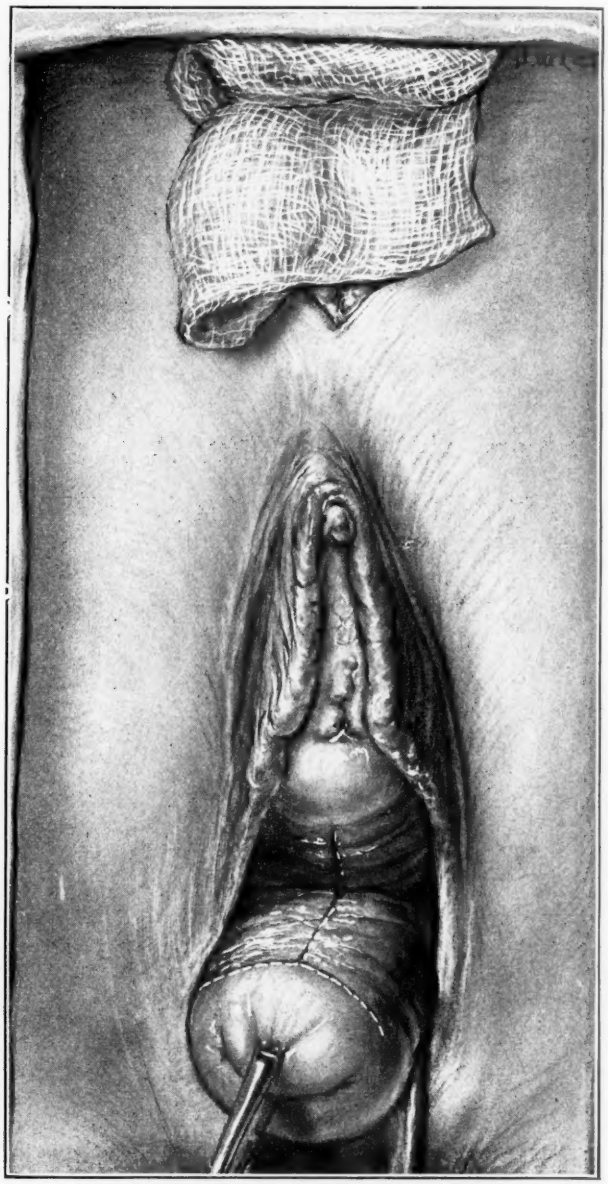

Fig. 6.—Incision for exposure of the suburethral space for reception of the pyramidoplasty straps, and for interposing the uterus beneath the bladder.

worked more deeply, so as to keep beneath these muscles and bring them along with the flap. Then holding the flap in a vertical position we cut down along its midline in order to form two fasciomuscular flaps. These flaps were dropped in the lower end of the wound and covered with gauze wet with salt solution. The upper portion

of the abdominal wound was closed by bringing the rectus muscles and fascia together in the midline with whipped interrupted twenty-day No. 2 chromic catgut. Then several No. 2 plain catgut sutures closed the fat layers. Next, beginning at the upper end of the wound, a subcutaneous silver wire suture was used to close the

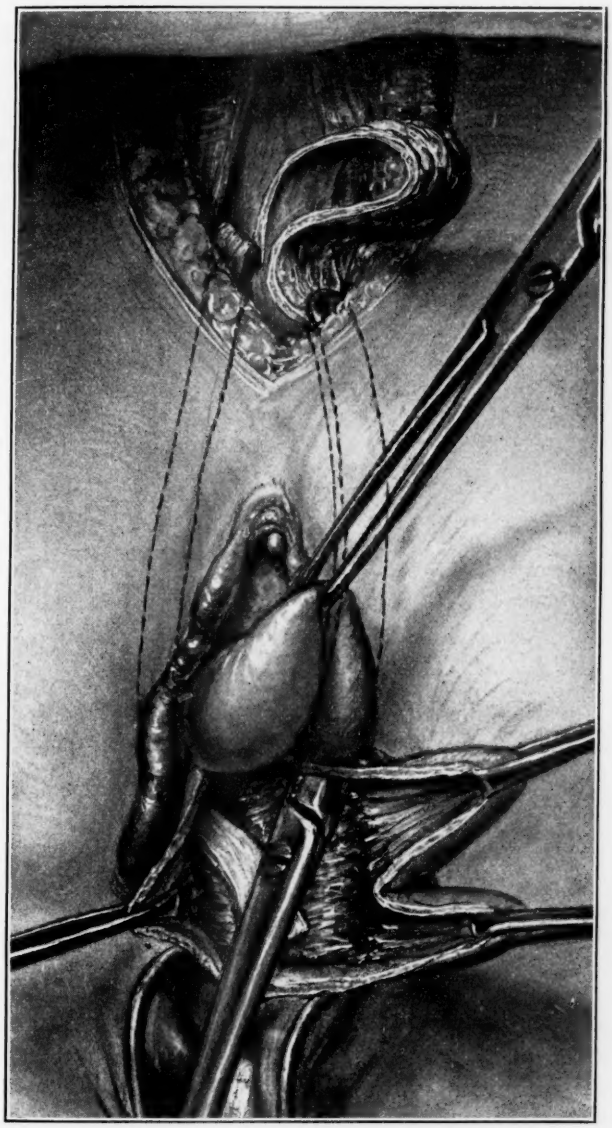

Fig. 7.—Pyramidoplasty straps being drawn through the subcutaneous tunnels to the suburethral space.

skin down to a point about opposite the upper ends of the pyramidales. From the perineal approach we performed the interposition operation which was meant to do away with the cystocele and to bring up the fundus snugly beneath the urethra. Grasping the external end of the urethra with Allis clip and the cervix with the four-prong tenaculum we carried a midline incision down the anterior vaginal wall,

beginning near the external urethral orifice and encircling the anterior aspect of the cervix (Fig. 6). We next lifted up triangular flaps of the anterior vaginal wall, beginning at the cervix and working upward, freeing the vagina from the bladder. As we reached the region beneath the urethra there was a good deal of old scar-tissue resulting from the childbirth injury. We were careful to keep close to the vaginal submucosa and avoid any remnants of muscle of the urethral sphincter that might be left.

The peritoneal cavity was then entered in front of the cervix and the bladder freed from the uterus and the tissues of the base of the broad ligaments. A wet gauze open sponge was pushed into the depths of the wound on the anterior wall of the uterus.

Next we brought down the rectus flaps and crossed them beneath the urethra (Fig. 7). The tissues alongside of the urethra and beneath the pubic arch were dense and almost of a cartilaginous character, and it seemed best to avoid exposing them with an open incision. The fat of the mons veneris was thick and an incision through it would have added to the dangers of postoperative wound infection.

For these reasons we modified the Miller method which extends the abdominal incision downwards through the Mons and through one labium majus and labium minus and connects with the suburethral incision. We simply took a curved Kelly clamp and beginning opposite the middle of the urethra we inserted the clamp first toward the right side, keeping close to the deep fascia over the pubic bone and directing the clamp upward. Its tip came out above the pubes in the lower end of the original abdominal incision. The clamp grasped the right rectus flap and dragged it back through this tunnel and then dropped it with its former upper end resting beneath the urethra. The same procedure was carried out on the left side. We found that our flaps were about 3 cm. longer than was necessary for allowing them to meet in the midline beneath the urethra (Fig. 8, *a*). We crossed the flaps in the form of an X, attaching first their upper edges together and taking up a bite of the suburethral tissues, after which the lower edge of the X was fastened in the same way to the suburethral tissues at a slightly higher point on the urethra (Fig. 8, *b*). This was done with fine linen thread. Then the redundant ends of the flaps were fastened to the subpubic tissues on either side, the flaps thus making a complete cross beneath the urethra (Fig. 8, *c*).

We then tested the effect on the urethra by passing a Kelly clamp into the urethral canal. Earlier in the operation any pressure on the bladder had caused the urethra to leak freely with urine, and a Kelly clamp would drop into the bladder almost of its own weight. But, now a Kelly clamp when being introduced into the bladder, met a distinct obstruction about midway in the urethra and had to be manipulated and slightly pushed before it would enter. We then tried an ordinary glass catheter and this met with a distinct obstruction as it passed through the urethra. A large quantity of urine drained off through the catheter.

The gauze drain, which had been pushed into the peritoneum, was now removed. The uterus was grasped on its anterior wall with tenaculum forceps and drawn forward through the peritoneal opening. With the index finger the uterovesical edge of peritoneum was pulled into the wound and attached on the anterior aspect of the dome of the uterus. Then the uterus was brought snugly forward beneath the urethra by two interrupted twenty-day catgut sutures going through the edge of the vaginal wall, grasping the anterior face of the uterus and coming out through the opposite edge of the vaginal wall.

We then trimmed off a triangle of excess vaginal wall on either side just anterior to the cervix and finished closing the anterior vaginal wall with interrupted twenty-day catgut sutures, each grasping the anterior face of the uterus and cervix as we worked downwards. Between the lower interrupted sutures a one-inch iodoform

gauze was placed in the broad ligament spaces on the anterior face of the cervix to offer temporary drainage.

The moderate rectocele was then repaired by making a transverse incision on the lower edge of the fourchet and dissecting up the posterior vaginal wall from in front of the rectum to expose the edges of the levator ani. These edges were brought together in the midline with a figure-of-8 of twenty-day catgut. Then a twenty-day catgut was used as a crown suture. Before tying this crown suture, we

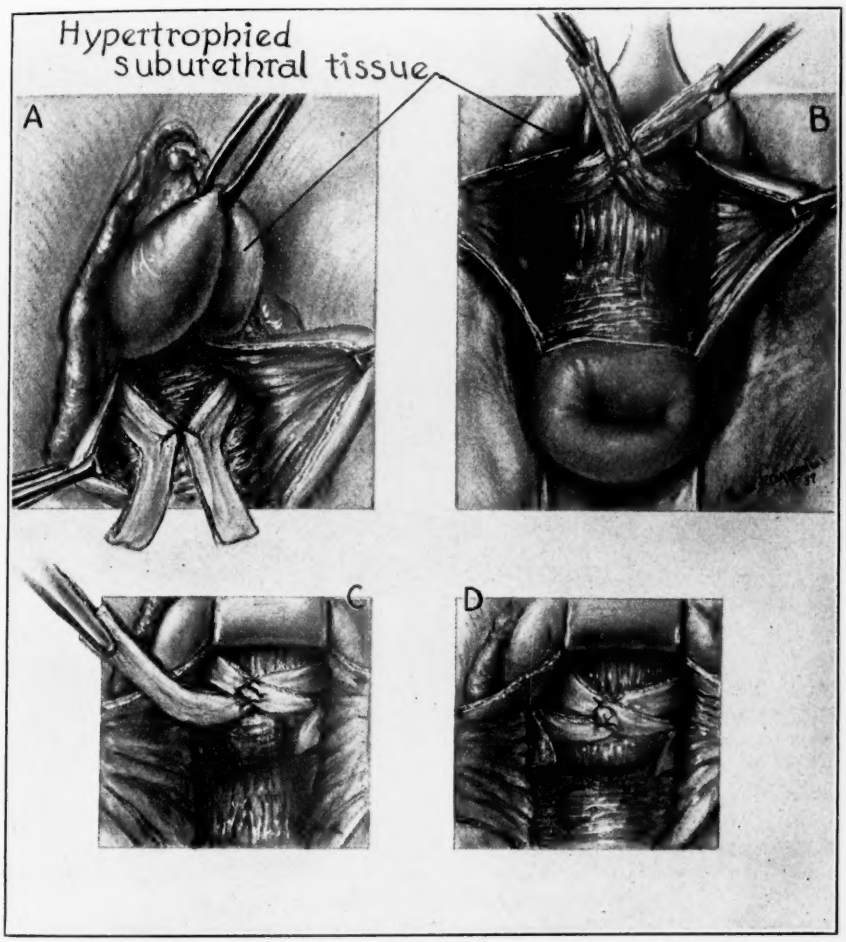

Fig. 8.—Straps crossed beneath the urethra, and outer ends fixed to the subpubic periosteum.

set three plain catgut sutures through and through from the sides, picking up the floor of the perineal body to close all dead spaces. These were first tied, and last of all the crown suture.

The iodoform gauze draining the broad ligament spaces was brought out to the vulva and plain sterile gauze was packed beside it in the vaginal channel. Both these gauzes were to be removed on the third day. A No. 9 male catheter was passed into the bladder and strapped on the inner side of the thigh for permanent drainage of the bladder (Fig. 9). The operation was completed by closing the lower end of the abdominal incision.

Postoperative History.—Convalescence was prompt, all the wounds healing normally. The urethral catheter was removed at the end of one week, after which the patient had perfect control up until the nineteenth day, when there was a slight unexplained leakage after she had been about the ward in a wheel chair for about two hours.

About ten days after the operation the patient complained of pain and soreness in the region of the left kidney. This reminded her of attacks she had had two or three years previously, particularly after getting her feet wet or catching cold. On

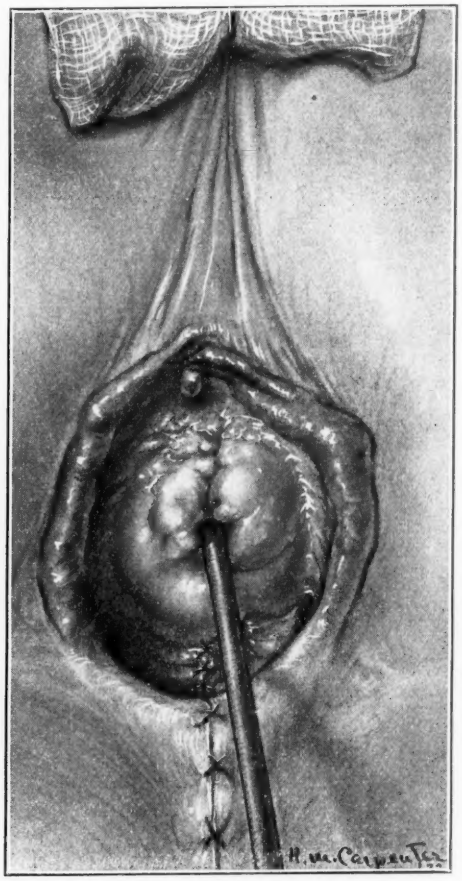

Fig. 9.—Final closure of operative wounds. Male catheter to be strapped to the inner thigh.

several occasions during our studies of her case she had complained of abdominal and pelvic pains which led us to suspect the presence of bilateral ureteral stricture, and on each of these occasions examination revealed tenderness over the ureters in the pelvic brim and broad ligament regions. On Feb. 8, 1937, a two-hour intravenous phenolsulphonephthalein test showed 1,000 c.c., 75 per cent of dye; blood pressure 105/80; Hb 85 per cent; white blood cells 6,360. Urinalysis, 1,005, acid, sugar 0, albumin 0; micro. 0. Culture from bladder, gram-negative bacillus, colon group.

A test of the left ureter with a No. 11 Fr. bulb near the catheter tip revealed apparent stricture in the upper ureter and again in the broad ligament region. A test of the right ureter on February 10th showed stricture in the broad ligament region.

The urine from each kidney was negative for leucocytes but on a slant agar tube there grew numerous colonies identified as belonging to the colon group.

A grip epidemic was prevalent in Baltimore at this time and the patient had a slight head cold at the time of our investigation of the ureters. The day after our last investigation her temperature reached 102.8° and this was thought to be due to a moderate left side pyelitis following the ureteral trauma in the presence of a renal bacilluria. However, on February 12 and 13 the temperature ranged between 101° and 105°, and there were typical signs of moderate consolidation in the left lung. There was slight loss of urinary control during these two days of high temperature. Blood cultures were negative. The temperature reached normal on February 16, but registered 102° on February 20 and at this time there were signs of acute pharyngitis and malar sinusitis. The temperature remained on the normal line from February 26 until the patient's dismissal on March 6. During the final days of hospital convalescence the patient, while sitting, or walking about the ward, had occasional slight leakage but controlled this promptly by contraction of the abdominal muscles.

She returned at our request on April 12, and reported that during her first week at home there was occasional slight leakage which she could readily control. A few days later she lifted her 32-pound boy and felt something give way in the region of the pelvis and after that she had no real control. At night she retained the urine for about four hours and then awakened spontaneously and voided without loss of control, but while at her housework in the daytime she had to wear a pad and did not void voluntarily at any time.

I had neglected to warn the patient against coitus for a definite period after returning home, and my first thought after hearing of the failure of the operation was that the pyramidoplasty straps may have been broken down during coitus. The patient stated, however, that coitus had not been resumed until after the bladder control had been lost. I believe that control can be restored by the comparatively simple operation of exposing the field beneath the urethra and then dissecting out and shortening the fascial straps.

Reference to Fig. 8 shows that the straps at their point of crossing were fastened together by two linen sutures, each of which was attached to the suburethral tissues, and that the end of each strap was then fixed to the deep fascia beneath the pubic bone. In a future operation I plan to detach the straps at the X crossing and carry each one independently across to its fixation in the subpubic fascia. Each strap will be shortened and given as snug a lift against the urethra as seems feasible. By this method it is quite conceivable that if an accident were to happen to one strap, the other would continue to function with complete control.

When last seen on May 7, the patient expressed the desire to wait until October for another operation. This conformed with my wishes, for plastic work about the urethra or bladder should not be attempted at too short intervals. This also gives ample time for a few more ureteral dilatations which will mean much for the patient's future health.

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DISCUSSION

DR. NORMAN F. MILLER, ANN ARBOR, MICH.—The paper lends itself to discussion from two points of view, first the obstetric and second the gynecologic. Such tremendous trauma as a result of spontaneous birth seems most unusual. I am led to ask whether any use was made of a powerful stimulant, such as pituitrin? I have seen one example of trauma of this extent. This occurred in a young woman as a result of a horseback accident. The girl suffered an injury very similar to the one described by Dr. Hunner.

In some similar cases, not with such extensive trauma, we have corrected the incontinence by various means, by repair of the anterior vaginal wall, and occasionally by the interposition operation. Where we have failed by one method or another we have resorted to a modification of the Goebell-Stoeckel operation. During the past six or seven years we have used it a number of times. We have constantly changed the technique. The difficulty reported by Dr. Hunner has also occurred in our experience and we have changed from the original modification as reported by me in 1931. I believe this operation has much to recommend it in occasional cases.

I believe that we as gynecologists must seriously consider the problem of restoring urinary control in women afflicted with this difficulty. It is surprising the number of individuals who complain of varying degrees of incontinence, particularly older women.

DR. GEORGE GRAY WARD, NEW YORK, N.Y.—I have had a similar case of lack of control which I successfully cured by utilizing a procedure used abroad a good deal with success and known as the Martius operation. It is simpler than the operation Dr. Hunner used. The bulbocavernosus and ischiocavernosus muscles which fuse together in a common tendon near the clitoris are severed at that point, and the two united muscles are brought under the reconstructed urethra and attached to the opposite pubic ramus. In some instances the muscles of both sides are used. This has given very satisfactory results.

Dr. Miller stressed the fact that so many women have incontinence when sneezing or coughing. That is a very common condition. Dr. Kennedy of my staff has been making some interesting studies with the x-ray to show the muscular control of the urethra and has devised a procedure which is under trial and which has been successful in some cases.

DR. HUNNER (closing).—I have no explanation of how this accident happened. The patient had had no drugs to hasten labor. I assume that the head was engaged so long that there had been injury from pressure on the tissues posterior to the symphysis, making it easy for the head or shoulders to sweep them down at the time of birth.

The use of the vaginal muscles did appeal to me very strongly in this case, but the left bulbocavernosus was cut across in the original injury destroying its upper third at least, and I was very much afraid that probably both of them had been pretty well detached from their nerve supply and were not particularly available in this case.

To use fascial straps from muscles having an uninjured nerve supply seemed safer, and in this case, with its sagging urethra, the symphysis arch offered a counterpoint of pressure for the tension of the pyramidalis straps.

BIOLOGIC AND CLINICAL IMPORT OF VULVOVAGINAL MYCOSES*

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PATIENTS are primarily interested in the relief of distress. While progressive physicians are interested in symptoms, they are concerned with the improvement of diagnostic and therapeutic methods as well as a better understanding of the entire disease process. Although the yeast-like fungi (monilia and cryptococci in particular) have long been recognized as etiologic agents of vulvovaginal mycosis, the frequency of the disease, predisposing conditions, improvements in therapy, and mode of action of the organisms have been more completely investigated recently. Perhaps through a better understanding of the biologic action of these organisms one may find avenues for approaching other problems. Only the monilia and cryptococci are under consideration here, though the terms oidium and torula, respectively, are at times incorrectly substituted.

CLASSIFICATION AND IDENTIFICATION

The total number of the yeast-like strains with pathogenic propensity is still unestablished. Furthermore, the taxonomy is chaotic. The term monilia as used here includes those strains known by Benham[1] and others as *M. albicans, M. candida,* etc., or by Stovall and Bubolz[2] as Type 1, 2, and 3. Because endomyces and saccharomyces are discussed in the current literature along with the monilia and cryptococci, Table I may aid in dividing these groups. Monilia develop mycelia and conidia but no spores, while cryptococci have conidia only and no spores. The conidia appear within twenty-four to forty-eight hours in Sabouraud's culture medium. Mycelia may not develop for days on this medium and infrequently special media with prolonged incubation may be required to bring them out. Likewise, asci- or endospores of endomyces and saccharomyces may develop slowly even upon special media. Benham,[1] and Benham and coworkers,[3] Stovall and Bubolz,[2] and others have described these procedures fully. The former group of investigators recommend the giant colony and microscopic appearance for identification, while the latter urge the use of the cultural characters in galactose, saccharose, lactose and calcium milk especially for the types of monilia.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

Such detail classification is unnecessary in routine diagnosis. Hopkins and Hesseltine[4] found atypical fermentation in a few strains of monilia and, therefore, suggested that both the cultural reactions and microscopic morphology be utilized where monilial strain identification is desired. They concluded also that since organic acids were unknown as end-products the difference between acid or acid and gas in sugar fermentation represented only a difference in degree. Moreover, the size of the inoculum may alter these reactions appreciably. Fig. 1 shows degrees of gas production.

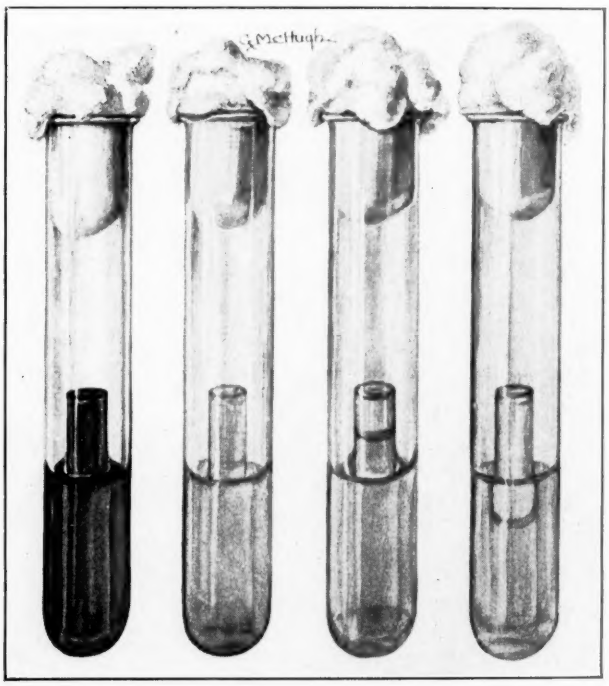

Fig. 1.—Fermentation tubes with bromcresol purple indicator. Tubes one to four read from left to right. (*1*) No fermentation. (*2*) Acid but no gas production. (*3* and *4*) Show different degrees of gas production.

PATHOGENICITY

Plass, Hesseltine and Borts[5] reviewed the literature up to 1931. Their own data indicated that pregnancy and diabetes mellitus were predisposing conditions for mycotic vulvovaginitis, and demonstrated convincingly that the sporadic oral thrush in the newborn was in all likelihood the result of contamination from its mother's fungus-infected vagina. Their description of the clinical appearance, symptoms, and diagnostic methods is complete. In 1934 by fulfilling Koch's postulate these teachers[6] proved that these organisms were pathogenic. It was stated then (and the importance was stressed) that certain patients of the experimentally inoculated group failed to develop the disease, even

though the organism might be harbored for a considerable period. This observation supports the view that mycotic carriers do exist. So far, endomyces have not been definitely found in the vagina, and saccharomyces are supposed to be nonpathogenic.

TABLE I. MICROSCOPIC MORPHOLOGY

	MYCELIA	CONIDIA	ENDOSPORES
Monilia	Present	Present	Absent
Cryptococci	Absent	Present	Absent
Saccharomyces	Rudimentary only	Present	Present
Endomyces	Present	Present	Present

Differential Cultural Characteristics

		GALACTOSE	SACCHAROSE	LACTOSE	CALC. MILK
Monilia					
Type I	Stovall & Bubolz	Acid	Acid	0	0
Type II	Stovall & Bubolz	Acid gas	Acid	0	Coagulation
Type III	Stovall & Bubolz	Acid gas	Acid gas	0	0
Endomyces		Acid gas	Acid gas	Acid gas	0
Cryptococci		0	0	0	0

INCIDENCE

Table II presents a varied incidence of fungi in the adult human vagina. The patients of Plass and others[7] at the University of Iowa were mostly indigents from rural communities. In contrast, the patients studied by Woodruff, Hesseltine and Phillips[8, 9] at the University of Chicago were almost solely urban. The incidences in the obstetric patients varied in Chicago from about 15 per cent at the Chicago Lying-in Clinic to 41 per cent in the colored patients at one of the Chicago Lying-in dispensaries. The white patients at this same dispensary had 33 per cent positive cultures, a frequency not much lower than in the University of Iowa series. Positive cultures are found far more commonly in patients complaining of vulvar irritation than in those who

TABLE II. INCIDENCE OF FUNGI IN PREGNANT AND NONPREGNANT PATIENTS OF VARIOUS TYPES

	PREGNANT			NOT PREGNANT		
	TYPE OF PATIENT	TOTAL CASES	POSITIVE CULTURES	TYPE OF PATIENT	TOTAL CASES	POSITIVE CULTURES
Plass, Borts, Hesseltine (S.V.I.)	Hospital ward	232	87 (37.5%)	Hospital ward	320	35 (11%)
		48 vulval irritation	27 (56.0%)		118 vulval irritation	21 (18%)
		184 no irrit.	60 (32.0%)		202 no irrit.	14 (7%)
Woodruff Hesseltine Phillips (U. of C.)	Lying-In Hospital	152	22 (14.5%)	Univ. Health Service	37	6 (16%)
	Stockyards (white)	150	50 (33.0%)	Douglas Smith Found.	73	8 (11%)
	Stockyards (colored)	100	41 (41.0%)			

are symptom free. If specific infections, as gonorrhea and trichomoniasis, are excluded, the relationship between symptoms and positive cultures is even more striking.

The incidences in the nonpregnant series are comparatively low, varying from 7 to 16 per cent. The Health Service group included only those with special complaints while the clients of the Douglas Smith Foundation were generally normal women. The deviation might be explained in part upon economic and hygienic levels, particularly since Todd[10] found 18.2 per cent of normal women harboring *M. albicans* in the mouth and throat and Benham and Hopkins[3] found 80 per cent of normal individuals to have yeast-like organisms in the mouth and feces.

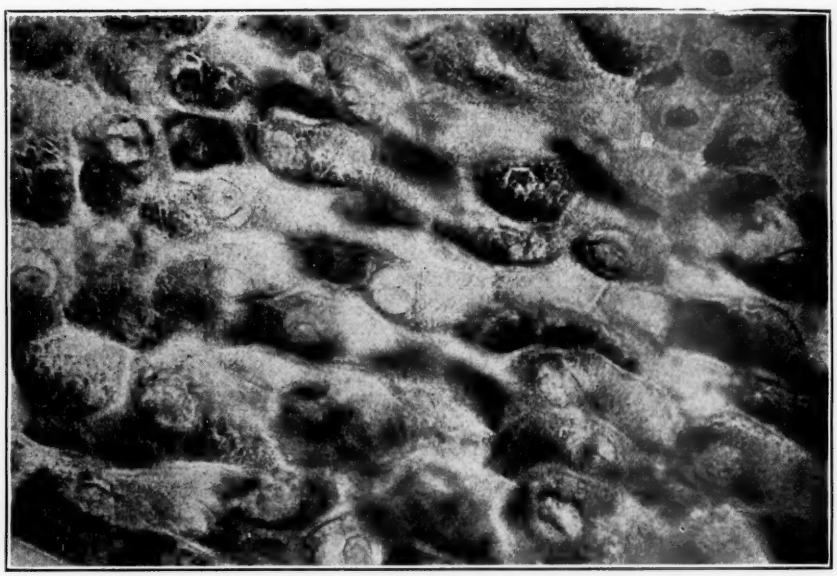

Fig. 2.—Glycogen-like material in vaginal epithelium demonstrated by Best carmine stain. ×1200. (After Adair and Hesseltine.)

Other sources of fungous infection, as the husband, clothes, or instruments, seem less likely.

INFLUENCE OF CHANGES IN THE VAGINAL EPITHELIUM

Adair and Hesseltine,[11] Karnaky,[12] Davis and Pearl,[13] and others have demonstrated the increased glycogen-like material in vaginal epithelium during pregnancy. The amount of this cellular content may be estimated microscopically when the biopsy specimen is fixed in absolute alcohol and stained according to the Best carmine technic. Fig. 2 shows a magnification of several hundred times and is self-explanatory. This increased source of carbohydrate, since it produces apparently a more favorable environment, may logically explain the increased incidence of fungi in the vagina. Conversely, the sudden loss of this material at

parturition leaves a less favorable environment and accounts for the sudden loss of symptoms. Peculiarly enough, immature girls are not known to have vaginal mycosis, and postmenopausal women rarely develop this disorder. The fact that glycogen-like material is present in lesser amounts in the premenaemic and postmenaemic vaginal epithelium lends additional support to the idea that its presence or absence is associated with an increase or decrease, respectively, in the mycotic infections. Adair and associates[11, 13] have described the histopathologic picture of the vaginal epithelium in normal patients and in those with mycosis, trichomoniasis, and senile vaginitis.

INFLUENCE OF DIABETES MELLITUS

One of the complications of diabetes mellitus in adult females has been a condition called "diabetic vulvitis." It is still stated by many that the glucose or irritating substances in the urine are responsible for the

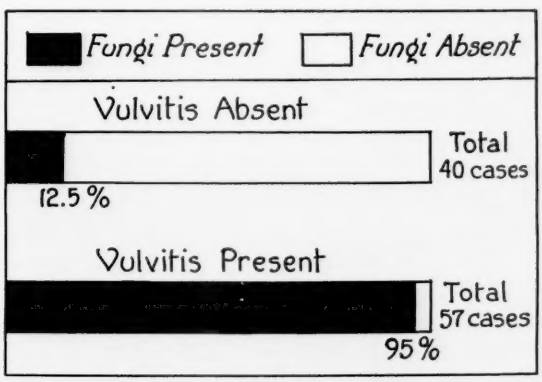

Fig. 3.—Incidence of fungi in diabetic women.

tissue reaction. The data of Plass and coworkers,[7] and Hesseltine's and Campbell's[14] are pooled to illustrate better the incidence of monilia and cryptococci. In all, 97 adult diabetic patients were cultured by the usual method for fungi (Fig. 3). One group consisted of 40 adult patients without vulvitis and only 5, or 12.5 per cent, had yeastlike organisms, an incidence about equal to that in the average group of nonpregnant women. On the other hand, 54, or 95 per cent, of the 57 with vulvitis netted positive cultures. One of the 3 negative patients was menstruating and the other 2 had used local medications before coming to the clinic. Unfortunately an opportunity for repeating these cultures did not occur.

The clinical appearance of this entity varies moderately, and at times may resemble certain stages of kraurosis (Taussig[15]) or chronic atrophic dermatitis (Adair and Davis[16]), although neither of these pictures (Figs. 4 and 5) illustrates this similarity well. Because a few diabetic females develop vulvitis and seek relief, it is imperative that the former disease be excluded in every patient suffering from mycotic vulvitis.

INFLUENCE OF GLUCOSE

If glucose did directly produce this tissue reaction, the clinical picture could be duplicated by washing the vulva with glucose solution (Table III). Consequently, nine patients free from vulvovaginal fungi and without local disease received 250 c.c. of a 10 per cent glucose (aqueous) solution as a vulval irrigation 5 times daily. These treatments were

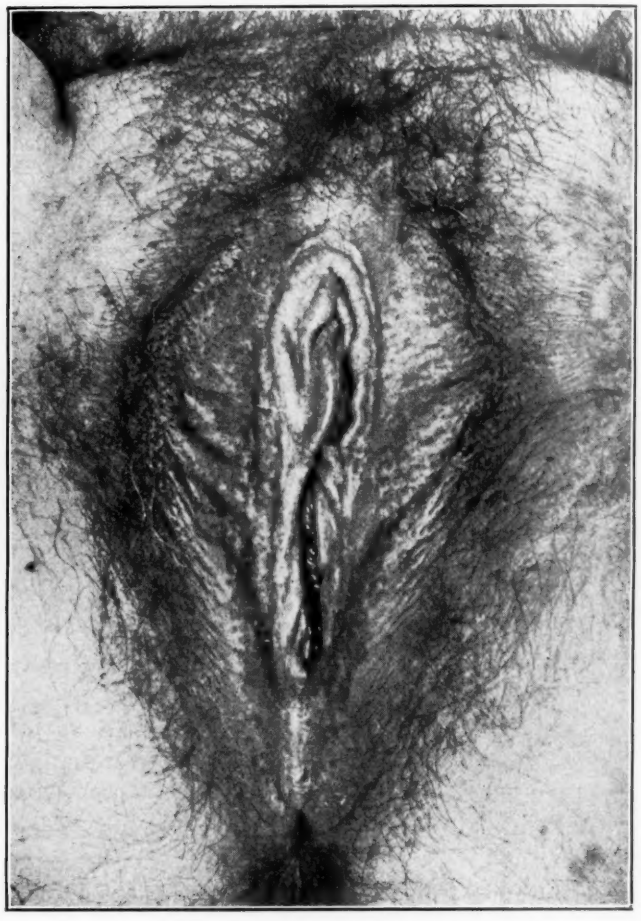

Fig. 4.—G. S. 79243. Diabetic patient with mycotic vulvitis involving the introitus, labia minora and medial aspect of labia majora.

given for three to twenty-two days (average ten) and in not one did symptoms develop or the tissue change. Five patients with mild vaginal mycosis or with fungi present in the absence of symptoms received the same treatments for one to five days (average three). All five of these women either developed a vulval mycosis or had the symptoms of an existing mycosis aggravated.

Another series was then treated by inserting 4 to 8 gm. of glucose into the vagina daily. Four fungus-free patients were treated seven to twenty-one days (average twelve days) without producing symptoms or tissue alteration. Five fungus carriers received the same treatment for two to seven days (average 4+ days), and every one had either an increase in severity of mycotic symptoms or induction of mycosis.

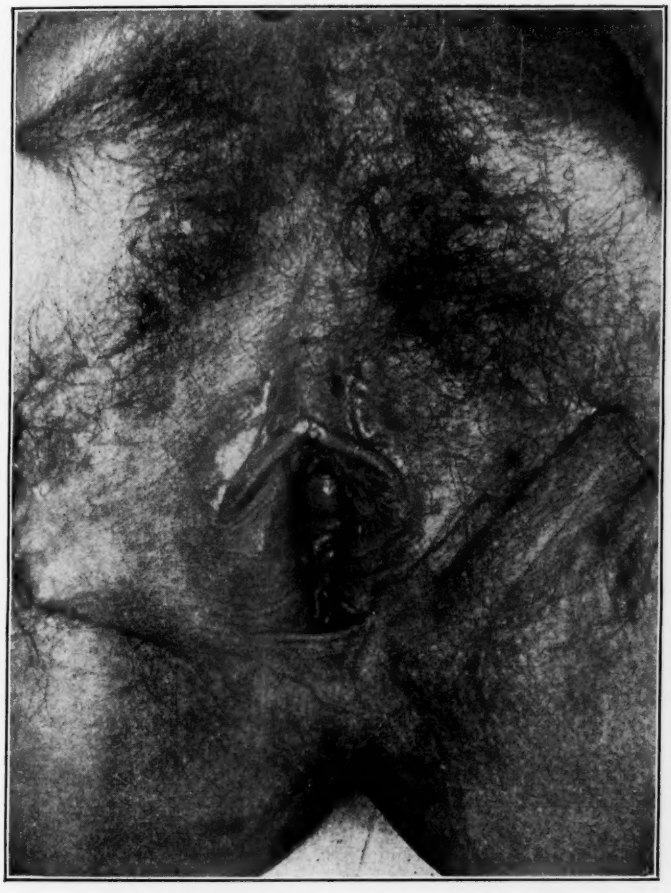

Fig. 5.—E. R. 76893. Mycotic vulvitis limited to labia minora with leucoplakia-like area in interlabial fold.

The influence of ketone bodies has not been evaluated. In any event glucose alone did not cause tissue reaction, but in the presence of fungi it increased or induced distress. Certainly then, glucose may provide a more favorable medium, and thus may indirectly be the cause of the vulvitis. Nevertheless, the fungi as shown above are the responsible agents. Therefore, since the term, "diabetic vulvitis" is incorrect, it is suggested that "mycotic vulvitis" or "fungous vulvitis" be substituted.

TABLE III. TISSUE REACTIONS OF VULVA AND VAGINA TO GLUCOSE IN NONDIABETIC WOMEN

DOSAGE	FUNGI	DAYS TREATED		TISSUE CHANGES OR SYMPTOMS
		PER PATIENT	AVERAGE	
125 grams daily wash	Absent (9 cases)	3-22	10+	None
125 grams daily wash	Present (5 cases)	1-5	3-	Increased or induced mycosis
Glucose powder	Absent (4 cases)	7-21	12	None
Glucose powder	Present (5 cases)	2-7	4+	Increased or induced mycosis

THERAPY

When the patients can receive vulvovaginal topical application 3 to 6 times a week, good results are obtained by using 1 or 2 per cent aqueous gentian violet solution as recommended by Plass and others.[5] Karnaky[12] advocates the use of a 5 per cent gentian violet in an alcoholic vehicle. The Chicago Lying-in Clinic patients object to such alcoholic concentration and often are unable to make frequent trips for local treatment. Several types of medicated douches failed to cure or even give much relief.

According to Hesseltine and Noonan,[17] beneficial results from acid and alkaline douches are highly improbable since these fungi tolerate pH ranges from 2.5 to 8.5 with increased cell growth. Even at a pH level of 9.5 the fungi were not destroyed promptly (Table IV).

TABLE IV. COLONY COUNT AFTER TWENTY-FOUR HOURS IN POURED PLATES (INOCULATIONS FROM TWENTY-TWO-HOUR GLUCOSE BROTH CULTURES). AVERAGE OF DUPLICATE TUBES. EACH 0.02 C.C. HAD 200 CELLS IN ORIGINAL INOCULATION

pH	F40	104	119	120	147	149	152	155	156	157
2.5	5,570	406	436	∝	821	∝	628	12	424	∝
5.5	∝*	∝	∝	∝	∝	∝	∝	∝	∝	∝
7.5	-	∝	3,904	-	∝	-	∝	2,745	∝	-
8.5	72	∝	1,384	∝	∝	∝	∝	2,170	2,500	1,700

* = not run ∝ = innumerable (After Hesseltine and Noonan.)

Hesseltine and Hopkins[18, 19] studied 86 materials for fungicidal potency. The following general groups indicate the comprehensive nature of the study: 11 acids, such as picric and salicylic; 10 dyes; 24 halogens, as element and combined iodines, organic and inorganic chlorine; 23 other metallic compounds, as arsenicals, mercurials, etc.; 11 other organic substances, as cresol, thymol, etc.; and 7 vehicles. When human serum and cells were added to the test solutions only a few substances warranted further study. By testing the fungicidal action on several yeastlike strains, element iodine was demonstrated to be the most potent and consistent agent. This confirms the reports of Emmons,[20] and Woodward, Kingery and Williams.[21] However, iodine as such is too irritating in the necessary dosage for vaginal therapy. Dieckmann and Hesseltine[22] found the liberated iodine from potassium iodide

and potassium iodate a potent fungicide. The equation in Table V gives the chemical reaction. In vivo the vaginal acids are used to complete the reaction. To carry each mole of iodine freed, a mole of potassium iodide is necessary. Thus 8 moles instead of 5 of potassium iodide to one of potassium iodate is the correct ratio. By weight this is 6.2 to 1, and the theoretical yield is 49.3 per cent iodine liberated. Since this chemical reaction in solution is sudden, and iodine is prone to burn,

TABLE V. IODINE LIBERATED FOR VAGINAL FUNGICIDAL THERAPY

$KIO_3 + 5KI + 6HCl = 6KCl + 3H_2O + 3I_2$

To keep Iodine in solution one mole of KI is added for each mole of Iodine liberated

$1KIO_3 + 8KI$ yields theoretically 49.3% by weight I_2

Approximate molar weights and ratio per unit weight

$1KIO_3(214) : 8KI(1328) :: 1 : 6.2$

The vaginal acids are utilized to complete this reaction

this mixture is diluted with neutral kaolin and dispensed in gelatin capsules. To guard against the premature liberation of iodine by acid impurities with the kaolin, this diluent is treated with ammonia and then dried to remove the excess. Capsules of 00 or 000 size contain approximately 0.125 gm. of the potassium iodide-potassium iodate mixture. The bulk of the content is kaolin. This allows for gradual solution and thus a gradual liberation of iodine over a longer period. Better results than with weekly or semiweekly application of gentian violet have been obtained by painting the vagina with diluted Lugol's solution (using the strongest concentration the patient can tolerate without discomfort, usually one-fourth strength) once a week, and the patient inserting 2 of these capsules in the vagina each night. Table VI indicates that generally patients can be cured within a period of several days or a few weeks. The results have been about the same for the pregnant and nonpregnant patient. The improved patients either discontinued therapy or delivered before completion of treatments.

The problem is not only to cure but to prevent re-infections. Further study is in progress along both of these lines. When and if patients receive treatment as Plass and others recommend,[5] there is no particular

TABLE VI. RESULTS OF POTASSIUM IODATE—POTASSIUM IODIDE AS FUNGICIDAL AGENTS

PATIENTS		TREATMENTS		RESULTS
NO.	TYPE	NUMBER	AVERAGE	
20	Ob.	1-9	3.5	15 Cured 5 Relieved
8	Gyn.	2-6	3.4	7 Cured 1 Relieved

reason for another method. Our data so far do not reveal any particularly promising combined iodine preparation. Perhaps in vivo response may be somewhat different from in vitro. Satisfactory means

of controlling the vaginal glycogen-like material in pregnancy remains undiscovered, and even such an alteration might predispose to other complications more serious.

BIOLOGIC ACTION

Perhaps the metabolic behavior of these yeastlike organisms may reveal an entirely different approach, or at least aid in a better understanding of this and similar disease processes.

The substance producing or mechanism resulting in irritation (pruritus primarily) and tissue reaction is unestablished.

Neuberg and his coworkers[23] have established some fermentation schemes of the yeasts on glucose. Their data show an oxido-reduction process, which appears to be simultaneous and continuous (Table VII). Tautomeric shifts are described also. Since they found 5 types of fermentation (Table VIII) one may anticipate others, especially in vivo.

TABLE VII. FERMENTATION SCHEMES

Type I—Neuberg

(a) $C_6H_{12}O_6 = 2H_2O + 2CH_2{:}C(OH)\cdot CHO$ (methylglyoxal)

(b) $CH_2{:}C(OH)\cdot CHO + H_2 + H_2O = CH_2(OH)\cdot CH(OH)\cdot CH_2(OH)$ (glycerine)

$CH_2{:}C(OH)\cdot CHO + O = CH_2{:}C(OH)\cdot COOH$ (pyruvic acid)

(c) $CH_3\cdot CO\cdot COOH = CO_2 + CH_3\cdot CHO$ (acetaldehyde)

(d) $CH_3\cdot CO\cdot CHO + O = CH_3\cdot CO\cdot COOH$ (pyruvic acid)

$CH_3\cdot CHO + H_2 = CH_3CH_2OH$ (ethyl alcohol)

TABLE VIII. FERMENTATION SCHEMES

Type II—Neuberg and Reinfurth

$$C_6H_{12}O_6 = \underset{\text{(acetaldehyde)}}{CH_3\cdot CHO} + CO_2 + \underset{\text{(glycerine)}}{C_3H_8O_3}$$

Type III—Neuberg and Hirsch

$$2C_6H_{12}O_6 + H_2O = \underset{\text{(glycerine)}}{2C_3H_8O_3} + 2CO_2 + C_2H_5OH + \underset{\text{(acetic acid)}}{CH_3\cdot COOH}$$

Type IV—Neuberg and Kobel

$$C_6H_{12}O_6 = \underset{\text{(pyruvic acid)}}{CH_3\cdot CO\cdot COOH} + \underset{\text{(glycerine)}}{CH_2OH\cdot CHOH\cdot CH_2OH}$$

Type V—Neuberg and Kobel

$$C_6H_{12}O_6 = 2H_2O + 2CH_3\cdot CO\cdot COOH \text{ (pyruvic acid)}$$

Nevertheless, some of those intermediary products may well be responsible, as acetaldehyde or pyruvic acid, for the symptoms and tissue reaction of vulvovaginal mycosis. In Type I fermentation, water and the enolic form of methylglyoxal are first produced from glucose. One molecule of methylglyoxal is reduced and hydrolized to glycerin while another is oxidized forming enolic pyruvic acid. After a shift to the

keto form, pyruvic acid yields carbon dioxide and acetaldehyde. A keto methylglyoxal and acetaldehyde are oxidized and reduced respectively into pyruvic acid and ethyl alcohol. Thus the process continues. Types 2, 3, 4, and 5 yield these products and acetic acid by other schemes.

Friedemann and Stenhouse[24] found that pathogenic monilia and cryptococci produced ethyl alcohol as readily as brewers' yeast. This observation suggests that the monilia and cryptococci may have a similar biologic action, but with a trend toward the production of particular intermediary or end-products which are responsible for the clinical entity. Since some features of certain stages of kraurosis and some types of mycotic vulvitis are similar, one may ask if there is not the possibility that in mycosis the precipitating factor is extrinsic and in kraurosis it is intrinsic.

CONCLUSIONS

1. Some of the recent contributions to monilial and cryptococcic vulvovaginal mycosis are reviewed.

2. A method requiring fewer office visits for treating vaginal mycosis is described.

3. It is emphasized that the term "diabetic vulvitis" is incorrect, since it is apparently a mycotic infection, and it is suggested that "mycotic vulvitis" or "fungous vulvitis" be used instead.

4. Glucose as such causes no irritation but produces a more favorable medium for the monilia and cryptococci.

5. Every patient with mycotic vulvitis should be examined for diabetes mellitus, and every diabetic patient with vulvar symptoms should be examined for mycotic infection.

6. The similarity of certain stages of mycotic vulvitis to kraurosis is mentioned.

7. Neuberg and coworkers' scheme illustrating mechanisms of fermentation of glucose by fungi is discussed in relation to biologic behavior. Such intermediary products as acetaldehyde or pyruvic acid may be responsible for the symptoms and tissue changes.

8. It is suggested that the fungi produce the precipitating factor extrinsically for the tissue reaction, while in such diseases as kraurosis it may possibly be intrinsically liberated.

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DISCUSSION

DR. WILLARD R. COOKE, Galveston, Texas.—The determination of the importance of the cell-content of glycogen constitutes the most interesting and immediately practical phase of Dr. Hesseltine's work. There are four very commonly encountered conditions whose cardinal symptom is pruritus: trichomoniasis, the mycoses, senile and diabetic vaginitis. In each of these the mode of elimination of the causative factor differs widely, and some of the accepted modes of treatment of the one condition will make another worse. Trichomoniasis calls for treatment which brings about a low vaginal pH with an excess of glucose. Senile vaginitis is best treated with massive doses of estrin, which may create a high cell-content of glycogen. An excess of free glucose or of cell-glycogen creates an optimum condition for the growth of mycotic organisms. Hence it is necessary to make an accurate diagnosis before treatment is instituted.

In the case of mixed conditions, which are common, it is necessary to use good judgment in the choice and sequence of the therapeutic measures employed. We have found that it is best to eliminate the mycotic infection before proceeding to treat trichomoniasis with organic acid and glucose, or senile vaginitis with estrin. Fortunately, this is usually rather easy, through the use of gentian violet. Dr. Hesseltine's free-iodine treatment should be equally appropriate and represents a distinct advance in the management of persistent mycosis and the early stages of mixed conditions.

I am very glad to see that Dr. Hesseltine says that the exact identification of the mycotic organisms involved in a given case is unnecessary. Most doctors are rather inclined to "shy off" from the attempt to diagnose mycotic vaginitis, because they are under the impression that this requires an elaborate technical equipment. If the profession at large could be convinced of this mistaken idea, a great deal of unnecessary suffering could be eliminated.

Dr. Hesseltine's report of the relative frequency of mycotic infections in the pregnant, the nonpregnant, the premenstrual, and the adolescent groups, and in the pruritic and nonpruritic subgroups, coincide closely with our own observations. On the other hand, we have found mycotic vaginitis quite common in the immediate puerperium and in the pre- and postmenopausal groups.

DR. EVERETT D. PLASS, Iowa City, Ia.—We have now accumulated sufficient data to cause us to eliminate that old name of diabetic pruritus vulvae and to utilize the etiologic nomenclature. It has been shown beyond question that the fungi can produce vulvitis and vaginitis, and in diabetic patients, the irritative symptoms are due not to the presence of glucose in the urine, but rather to the growth of the fungi in the sugar. In these diabetics with vulvar irritation, relief can usually be given in one of two ways. Almost immediate relief can be produced by application of one of the fungicides, or the same result can be obtained in the long run by treating the diabetes.

We have continued using gentian violet because it is simple, is in itself nonirritating, and is generally effective. In the majority of our patients from one to three applications will give marked relief and sometimes effect a permanent cure. It is interesting, however, to know that in the more stubborn cases iodine preparations can be employed. We should bear in mind that there are available for vaginal insertion capsules which contain gentian violet. Hence even that form of therapy can be carried out by the patient independently.

The main problem in therapy for most patients is that of affording immediate relief and there is no question that gentian violet and the iodine preparations are effective in relieving irritation. The further problem of curing the patient completely is obviously difficult in some cases because of the possibility of reinfection. In the majority of our cases we have had no clue as to the mode of infection, and I am curious to know whether Dr. Hesseltine's recent studies have pointed in any way to the answer of that problem. In the wives of diabetic husbands, we sometimes find a very logical explanation for the mycotic infection of the wife since the husband may have a marked mycotic infection of the genital organs.

DR. ROBERT A. ROSS, DURHAM, N. C.—We have been impressed with the frequent findings of *Monilia albicans* unassociated with clinical manifestation. This led Jones to study the cultural and morphologic characteristics more closely, and he has established a new species which closely resembles albicans but does not give symptoms nearly so often. This strain has been named *Monilia stellatoidea.* It varies from the *Monilia albicans* in five definite ways. It does not produce acid in saccharose. It is similar in other fermentation tests. On slide culture it rarely produces chlamydospores. On the blood agar plate the culture is star-shaped. When injected in the rabbit it does not cause death. It will not agglutinate in *Monilia albicans* serum.

Where there is any doubt as to the causative factor in vulvovaginitis, we resort to an intradermal test. Where the monilia is the causative factor, a local reaction will develop within a few hours and persist for as long as forty-eight hours.

In the more refractory patients, that is, those who have been treated over a long period of time by many different agents, we have employed vaccine therapy. Usually a definite reactivation of the process in the vulva occurs and persists until the patient is desensitized.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—I would like to ask if Dr. Hesseltine has used sulfanilamide in the treatment of this condition.

DR. HESSELTINE (closing).—It is true, of course, that we do not have a safe and adequate way of controlling the glycogen content of the vaginal epithelium. Since this predisposing state cannot be avoided, curative and prophylactic means must be used.

As regards the possible sources of infection, Todd and others have found an 80 per cent frequency of fungi in the oral and intestinal tract. Thus a source through fecal contamination exists and is probable. Other patients may be carriers with the disease developing only when conditions are favorable.

I have not recommended the potassium iodide-potassium iodate mixture to replace gentian violet, so far it is recommended only for the patients that cannot be treated according to the ordinary method with gentian violet.

We have had no experience with sulfanilamide, the drug mentioned by Dr. Curtis. The mercurial, arsenical, and other compounds have been less efficacious fungicides. In vitro, at least, the element iodine possesses the greatest fungicidal potency.

ANALGESIA AND ANESTHESIA AND THEIR BEARING UPON THE PROBLEM OF SHORTENED LABOR*

ARTHUR H. BILL, M.D., CLEVELAND, OHIO

IT IS very interesting to note the reaction of members of the medical profession toward the question of painless labor at various times during the last two or three decades. There was the period during which either nothing was given to relieve pain or merely a little chloroform as the head was being born and when in national obstetrical society meetings there was bitter opposition to proposals for relief of pain, all kinds of arguments, some quite silly, being made against such proposals. In years following, a continually increasing number of obstetricians had a more or less favorable attitude toward painless labor and instead of opposition there were efforts to develop new methods for relief. Many were suggested, perhaps in most cases too much stress being laid upon the individual procedure, even to the extent of making it a fad for the laity. Much that is disgusting has been published in lay journals. More recently we have heard renewed opposition to painless labor in medical circles. Bad results of childbirth have been attributed to analgesia and anesthesia, when in reality they were due to bad judgment or technique of poorly trained physicians. Unfortunately this has been quoted in lay journals, all to give the laity a very wrong impression of the real facts and values. Through all these years my associates and I have continued, unswayed by these discussions, to relieve all pain of labor and delivery, from start to finish, to the fullest extent of our ability to do so. Painless labor is not an experiment nor has it been considered such at the Cleveland Maternity Hospital during the last twenty or twenty-five years. From the results obtained in a very large number of cases we have no doubt as to the safety and effectiveness of our relief methods and have never had any hesitancy about continuing them but have rather been amazed at groundless arguments against such procedures.

It would seem that in spite of some unfavorable opinion the real question today is not whether to make labor painless but how to do this in the best way. The chief mistake of those who have advocated any particular method has been the attempt to make of it a means of conducting the entire labor painlessly. For example one may advocate morphine-scopolamine, colonic ether, paraldehyde, the various barbiturates or avertin as if any one of these were a method in itself sufficient. No one

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is entirely satisfactory. They should all be thought of as adminstrations to be given preliminary to analgesia by inhalation methods and general anesthesia. They are only suitable for the first stage of labor. The latter part of labor is conducted in a far better way with inhalation anesthesia. In other words late in labor the degree of amnesia or anesthesia should be under the complete control of the anesthetist who can at will deepen or lighten the anesthesia according to the demands of the individual case and not be handicapped by the action of a drug which may produce deep hypnosis and will only be eliminated after a lapse of time. If the action of the drug which has been given to cause amnesia has practically or entirely worn off by the time of delivery there is a distinct advantage. The importance of this varies with the drug used being greater, perhaps, in the case of morphine-scopolamine than in the others but applies somewhat to all. The basis of our routine practice is, therefore, to consider medication as essentially suitable for the first stage or a little less and the general anesthetics for the second stage and latter part of the first stage.

There is much difference of opinion as to the relative merits of different forms of medication. In contrast to cases in which no relief is offered they are all good. However, after trying most of them, experience has given me more confidence in some than in others and our procedures are based upon this experience. I cannot find any method of premedication which is so uniformly satisfactory in cases of primiparas as morphine and scopolamine. In it I have found a method which does not interfere with the progress of labor and as we use it, is safe for mother and baby and very consistently leaves with the patient little or no recollection of the entire labor. The completeness of its action in this respect is not equalled by other medication. Criticism of scopolamine as a cause of fetal mortality is undoubtedly due to the manner in which it is used. I refer especially to attempts to make of it a method for conducting the entire labor and giving it in the second stage and in the most uncertain labors of multiparas. If this is done the babies will, in a certain number of cases, be in a state of serious apnea. Realizing its limitation in this respect we have adhered to a definite rule, that scopolamine should not be given within at least three hours of the expected time of birth. The observance of this rule has probably, to a very large extent been responsible for our uniformly good results from the use of scopolamine in more than 20,000 cases. When the three-hour rule is observed, the baby shows no serious apnea. We very frankly do not believe that we have lost any babies as the result of this procedure. It is seldom difficult to time the administration to conform to this rule. For example after the first three hypodermics, which are given forty-five minutes apart, $\frac{1}{400}$ gr. of scopolamine is given hypodermically every one and a half hours until discontinued. When the next dose is due, one

and a half hours have already elapsed and the decision as to whether or not to give the dose is based merely on an estimation that not much more than one and a half hours additional will pass before the birth. The decision is commonly made with the aid of a rectal examination.

The scheme of dosage is as follows:

Morphine gr. $\frac{1}{6}$	as soon as pains seem to hurt with no regard for the
Scopolamine gr. $\frac{1}{150}$	amount of dilatation.
Scopolamine gr. $\frac{1}{200}$	after forty-five minutes.
Scopolamine gr. $\frac{1}{400}$	after another forty-five minutes and every hour and a half thereafter until discontinued.

As a rule, morphine is not repeated but in some cases, after several doses of scopolamine have been given, if the pains are unusually hard and the patient seems likely to feel them, an additional $\frac{1}{6}$ gr. is given. This is, however, in the exceptional case.

It is apparent that the observance of the three-hour rule makes scopolamine quite impracticable for use in cases of multiparas and as much as I regret this I have not felt safe in using it in such cases. The exception is the occasional case in which with slow dilatation and a rigid cervix we may decide, after watching, that the labor will simulate that of a primipara. In these cases a single dose is sometimes given to supplement the other method which is being used.

While nothing quite takes the place of scopolamine for primiparas, there is not such a striking difference between some of the better methods to be used for multiparas. I refer chiefly to sodium amytal, pentobarbital, colonic ether and paraldehyde. I put them in this order, as in my opinion this is the way they should be rated. Sodium amytal is used at the Cleveland Maternity Hospital almost routinely as the medication for multiparas. There is very little difference between the action of sodium amytal and that of pentobarbital. Pentobarbital acts a little more quickly and wears off sooner. Therefore sodium amytal, the effect of which last longer, is to be preferred, for repetition of the dose will not as a rule be necessary. Sodium amytal also lends itself to combination with other sedatives far better. A maximum dose is not given. We do not vary the dose with the body weight but give 9 gr. at the beginning of labor. This would be an average dose and seems sufficient. It is given by mouth, but if an additional dose is necessary after several hours, it is given by rectum, usually being 6 gr. The effect ordinarily lasts at least three hours. In using sodium amytal in cases of multiparas, we do not fear fetal asphyxia and therefore, we do not observe the three-hour rule as in the use of scopolamine. We have no hesitation in giving sodium amytal before cesarean operations.

While results fairly comparable to those obtained from scopolamine are seen with sodium amytal, it cannot be said that there is as consist-

ently the same complete obliteration of the consciousness of the entire labor. In this respect we have, however, found it to be a method which gives more uniformly satisfactory results than either paraldehyde or colonic ether.

The effect of these various drugs upon the progress of labor as shown by tracings of uterine contractions was studied by Dodek and later by Moore while on my service at the Cleveland Maternity Hospital. Following is a brief summary on their findings.

In established labor scopolamine has no appreciable effect upon the uterine contractions. The initial dose which is combined with morphine will probably give a morphine action which is a moderate depression in the intensity of a few contractions. The action of morphine is quite variable, clinical experience being that it sometimes hastens dilatation. The slight and temporary effect is over by the time the next dose is given and the contractions become as strong as before and remain so while scopolamine alone is given in the subsequent doses.

Sodium amytal does not diminish the force of uterine contractions nor interfere with complete relaxation between them. Dilatation progresses very normally.

Colonic ether has very little effect upon the uterine contractions when combined with quinine. We use it supplementary to morphine and scopolamine or sodium amytal in some of the more prolonged labors in which, without it, inhalation anesthesia would be necessary over an impractical length of time. It is not often used as a primary medication and is limited to the first stage of labor.

The effect of paraldehyde is a temporary diminution of the intensity and duration of uterine contractions; however, this effect is usually quite brief, the contractions regaining their previous character within a half hour. Its sedative effect is quite variable in different patients.

The effect of avertin is a prolongation of the intervals between the contractions. Furthermore, its analgesic effect is of too short duration to make it worthy of serious consideration.

Comparing the effects of the first four, morphine and scopolamine, sodium amytal, colonic ether and paraldehyde, we cannot say that with any one of them there was enough interference with uterine contractions to make it unsuitable as an analgesic. Our selection of one in preference to another is therefore based largely on the consistency and completeness of its action in causing amnesia and analgesia.

Scopolamine and sodium amytal constitute the basic medication which we use for preliminary analgesia and are in therselves sufficient for this purpose in the average case. However, we use many combinations in the more difficult cases, according to their demands, and do not adhere strictly to the original method if the patient does not seem to be entirely relieved of pain.

As previously stated one should not depend upon medication entirely for the relief of pain. As the pains become harder, it is better to supplement this by inhalations of a general anesthetic given at first merely during the uterine contractions as analgesia, later on continued lightly between contractions and eventually deepened to anesthesia for the delivery. Clever administration of the general anesthetic is really the most important part of the conduct of painless labor. However, inhalation analgesia alone is not entirely satisfactory without the basic medication which tides over the interval between pains and has a decided quieting effect on the patient and does away with the disagreeable sensation of repeatedly going under and coming out of the anesthetic. The result of the combination is an unbroken period of amnesia. As the medication wears off later in labor, it is important that enough anesthetic be given to prevent the patient from at any time becoming conscious of what is going on and thus preventing any break in the continuity of the treatment. To give just enough anesthetic to relieve pain and not slow the labor is a real art, but is accomplished in a remarkable manner by an anesthetist also trained in obstetrics who has an understanding of the greatly varying action of the uterus in different labors and of the emergencies which may arise. We believe that the ideal anesthetist is the nurse anesthetist who has previously had responsibility in obstetric surgery.

The administration of ether for analgesia and only during contractions should be given with a closed cone so that a sufficient amount may be given in the shortest time. Drop methods are altogether too slow for this purpose. Much of the success also depends upon the alertness of the anesthetist in anticipating the pains. This is accomplished by keeping a hand on the patient's abdomen and applying the anesthetic as soon as the uterus begins to contract, which is usually before the patient shows any other evidences of the onset of pain. If the anesthetic is applied only after the patient complains of pain, it is too late to give satisfactory relief.

The proper choice of the anesthetic to be used in each case is important. From a strictly obstetric point of view, we may divide anesthetics into two classes, first, those which tend to cause relaxation of the uterus, and second, those which are relatively nonrelaxing. Both kinds should be available for use during labor. Ether is a good example of the first, while nitrous oxide and oxygen represent the second. We consider these the most satisfactory from the standpoint of safety and effectiveness. Tracings showed that when ether is given only for analgesia there is no appreciable effect on the uterine contractions. However, if ether is given to the point of surgical anesthesia, it is possible to stop the contractions entirely. Nitrous oxide caused no diminution of uterine contractions when used for analgesia, and even when the patient was under deep anesthesia, it was not possible to cause complete relaxation.

If there are no other indications or contraindications, the choice of anesthetic is made with this action in mind so as to adapt it to the individual case. For example if the pains are very strong and frequent or perhaps too strong, ether is given. If the pains are not very effectual and infrequent, nitrous oxide and oxygen is preferable.

Relief for pain is given to each patient as soon as she seems to suffer, with no regard to the amount of dilatation. As a rule it is not necessary for her to ask for analgesia for her wishes are anticipated. However, a patient who asks for relief is never told that she "must wait," that it is "not time to give anything" or that "the pains are not hard enough." We believe that the patient is the best judge of her sense of pain. A patient admitted to the hospital in hard labor is relieved by the quickest method which is inhalation. In some cases, chiefly primiparas, this is only temporary and may be discontinued for a varying period after the first stage medication becomes effective.

The following summary illustrates the average number of hours during which inhalation analgesia and anesthesia are used.

Inhalation analgesia and anesthesia as administered to 100 consecutive patients in labor, consisting of 25 private and 25 staff primiparas and 25 private and 25 staff multiparas.

PRIMIPARAS

Analgesia:

Nitrous oxide-oxygen	Ether
13 cases	37 cases
Average duration per case	Average duration per case
2 hours and 5 minutes	2 hours and 52 minutes

Anesthesia:

Nitrous oxide-oxygen	Nitrous oxide-oxygen-ether	Ether
2 cases	10 cases	38 cases
Average 33 minutes per case.	Average 50 minutes per case.	Average 38 minutes per case.

Average duration of labors 15 hours and 24 minutes

Average duration of inhalation analgesia and anesthesia per patient 3 hours and 18 minutes.

MULTIPARAS

Analgesia:

Nitrous oxide-oxygen	Ether
15 cases	35 cases
Average duration per case	Average duration per case
1 hour and 4 minutes	1 hour and 48 minutes

Anesthesia:

Nitrous oxide-oxygen	Nitrous oxide-oxygen-ether	Ether
2 cases	14 cases	34 cases
Average 43 minutes per case.	Average 37 minutes per case.	Average 27 minutes per case.

Average duration of labor 9 hours and 30 minutes.

Average duration of inhalation analgesia and anesthesia per patient 2 hours and 15 minutes.

We have seen benefits from the use of analgesia and anesthesia in labor considerably broader than the mere relief of pain. The convalescence of the patient is smoother and less accompanied by nervousness.

Many of the nervous symptoms of pregnancy, including nausea and vomiting, have undoubtedly been due to or aggravated by a dread of an event which the patient has been taught from girlhood to think of as a terrible ordeal. In a community in which the patient knows that she will not suffer during her labor, much of this is eliminated and her mental state is greatly improved. However, the outstanding advantage is seen in the control of the latter part of the labor and delivery by the anesthetist, who can by the proper selection of the anesthetic and the careful regulation of the amount administered control at will the force of the uterine contractions. The following typical cases illustrate the advantage of being always ready to diminish the force of or completely stop the contraction without delay when the baby shows signs of distress due to pressure. There is the occasional case in which, due to unusually forcible pains, the fetal heart becomes alarmingly slow, at first during a contraction and then continuously. Deeper anesthesia with ether will usually cause the fetal heart to return to normal by taking excessive pressure off the baby. I have seen some very striking examples of this kind in which there can be no doubt that the skillful administration of ether saved the baby's life. In such a case the fetal heart is counted constantly and the amount of ether given is regulated according to the heart rate. Fear of harm to the child from the anesthetic is all too common and unfounded. In most cases of fetal distress there is actual benefit from the administration of more anesthetic. This should, however, be of the more relaxing type (ether), and if it happens that nitrous oxide is being given at the time, change should be made to ether. In other words, fetal distress sometimes attributed to the anesthetic is on the contrary, invariably, due to the labor. Also consider the case in which, during hard second stage pains, there is an increased amount of bleeding accompanied by a variability of the fetal heart. The diagnosis is plain. The placenta is beginning to separate and there may be complete separation with the death of the fetus if contractions continue. The uterus should be immediately put to rest by complete surgical anesthesia and delivery accomplished. Other examples are the prolapsed cord and beginning contraction ring. In all of the cases in this group a relaxing anesthetic (ether) must be used. Nitrous oxide will not do.

The way in which the anesthetic is of great value to the obstetrician is well illustrated by our usual procedure in a forceps delivery. Contractions are allowed to go on until it is time to deliver. The patient is then relaxed for the local preparation, the ironing out of the perineum and for any necessary manipulation such as rotation of a head from a posterior position. The anesthetic is then decreased so that contractions will increase during the descent of the head. We lay great stress on this and make traction with forceps only during a uterine contraction.

The anesthetist keeps a hand on the patient's abdomen and announces the onset of each contraction. Simultaneously traction with forceps is then made. In this way the amount of pull needed is reduced at least 50 per cent. The amount of traction used in forceps delivery was studied by Dr. Burdette Wylie with the use of a "tractionometer." The average pull in cases of primiparas was 13.7 kg. and in cases of multiparas 10.03 kg. In the latter, however, there were many in which the pull was less than 5 kg. The figures correspond very closely to the estimated force of the uterine contractions. Therefore, without the aid of the contractions twice as much traction would be necessary. When the head is crowning, the anesthesia is deepened to the point of relaxation for the actual delivery and is then either discontinued temporarily or lightened for the third stage to again encourage contractions. For any necessary repair following delivery of the placenta there is ordinary continuous anesthesia.

Anesthesia given in the way described is not easy for the anesthetist, being much more complicated than that for the ordinary surgical operation, but contributes very greatly to the results, especially in the more difficult cases.

For this type of delivery nitrous oxide-oxygen is preferable to ether because of its lesser tendency to relax the uterus. However, even under light ether anesthesia contractions sufficient to enhance the traction force are seen. On the contrary in cases in which internal podalic version is to be performed, the use of nitrous oxide-oxygen is contraindicated, for the uterus is quite likely to contract during the version and make it a dangerous procedure. For such cases we use ether anesthesia.

Painless labor and shortened labor are sometimes discussed as if the latter were a natural sequence of the former. Undoubtedly those who speak of shortened labor are thinking of meddlesome and harmful interference. To analyse this question we must rightfully consider the first stage and the second stage separately. There can be no doubt that much of the bad obstetrics is due to attempts to terminate the labor before the cervix is fully dilated. The longer one practices obstetrics the more he respects the resistance of the cervix. In my opinion the cervix has been the cause of more stillbirths than has the bony pelvis. Attempts to deliver the baby before full dilatation except in most urgent cases constitute meddlesome interference. Probably one of the chief reasons why a doctor does this is to terminate the suffering of the patient, especially when influenced by the demands of the family to "do something." If the patient is not suffering there are usually no such demands and the physician is free to let the first stage run its course. It would seem that instead of relief of pain leading to this type of interference it is the surest way of avoiding it. The same principle could apply to the second stage, for whether there is spontaneous

birth or operative delivery depends more upon the judgment of the obstetrician than upon the anesthesia. I personally prefer to correct abnormalities of position such as occipitoposterior and deliver. When the head is in an anterior position, it is my custom to let it descend to the perineum, which it will do in a large percentage of cases, and then deliver by low or prophylactic forceps. I prefer to use prophylactic forceps not because the anesthetic makes it necessary, but because I believe that there are distinct advantages, including a better aseptic technique, more skillful control of the rapidity of the birth, and prevention of unnecessary prolonged pressure upon the child's head.

Something should be said about the often mentioned danger of anoxemia. Some examinations of both maternal and fetal blood at the time of delivery have been made by Dr. J. W. Mull at the Cleveland Maternity Hospital. They show that there is no anoxemia after ether anesthesia. In the use of nitrous oxide-oxygen anesthesia Eastman found that a mixture of 90-10 caused anoxemia which was serious for the baby while one of 85-15 caused no serious anoxemia. In our service this anesthetic is not given in a mixture less in oxygen than 80-20 which seems perfectly safe for the baby.

Danger of anesthetics contributing to postpartum hemorrhage, by causing too much relaxation of the uterus, may be avoided by medication. It is our routine practice for this purpose to give 1 c.c. of pituitary preparation as soon as the baby is born and an ampule of ergotrate, intramuscularly, as soon as the placenta is delivered.

There is a small group of cases, chiefly those with infection of the respiratory tract, in which the general anesthetics must be used with great caution or avoided. In these cases ether is avoided in any event and if the case is such as to forbid the use of nitrous oxide, as well, the usual medication may be followed by perineal nerve block with novocaine, the results being fairly satisfactory, though, of course, not at all comparable to those obtained from the use of general anesthetics.

Naturally it must be assumed that for conducting the type of labor here described there must be adequate facilities, usually found only in hospitals.

The summary which follows will illustrate results which may be obtained from the treatment herein described. It is a summary of the last 240 consecutive occipitoposterior cases which I have personally delivered from the time of a previous publication up to date. It would seem that occipitoposterior cases would serve well for purpose of illustration, because they are probably the most troublesome of all. In this series all of the patients were given analgesia and anesthesia both by medication and inhalation and the deliveries were all operative, being either rotation of the head by forceps followed by forceps delivery, or internal podalic version. The way in which varied combinations of medication are used is illustrated.

OCCIPITOPOSTERIOR

Primiparas	119
Multiparas	121
Total	240
Vertex L.O.P.	109
Vertex R.O.P.	131

AVERAGE DURATION OF LABOR

First Stage:

Primiparas	17.79 hr.
Multiparas	8.69 hr.

Second Stage:
58 minutes

MEMBRANES RUPTURED

Before onset of labor	28
At onset of labor	9
During first stage	72
During second stage and at delivery	112
Questionable	19

METHODS OF DELIVERY

Internal podalic version		125
Forceps rotation and delivery		115
High medium	9	
Medium	56	
Low or low med.	50	
Voorhees' bag		6
Episiotomy		89

ANALGESIA PRIMIPARAS

Morphine and Scopolamine

Plus ether	48
Plus colonic ether and ether	12
Plus sodium amytal, colonic ether and ether	4
Plus sodium amytal and ether	5
Plus nitrous oxide	41
Plus colonic ether and nitrous oxide	2
Varied	5

ANALGESIA MULTIPARAS

Sodium Amytal

Plus ether	56
Plus nitrous oxide	37
Plus colonic ether and ether	8
Plus colonic ether and nitrous oxide	2
Varied	2
Inhalation ether	13
Nitrous oxide and ether	5

ANESTHESIA FOR DELIVERY

Ether	149
Nitrous oxide	7
Nitrous oxide and ether	84
Total	240

MORTALITY

Maternal	0
Fetal corrected	0

2 died; both had congenital malformations incompatible with life

MORBIDITY

After first 24 hours postpartum, temp. 38° or over for two successive days—temp. not necessarily continuous.
13 cases—5.4%

MORBIDITY

1 Acute "cold"—Temperature on admission and 3 days
1 Mastitis. Temperature on 12th and 13th days
5 Pyelitis
1 Tonsillitis
5 Cause uncertain. Temp. of 38° on only two occasions. Normal afterward

From the results obtained in this series, it must be apparent that the medication and anesthesia had no deleterious effect upon either mother or child. On the contrary it would seem that the clever administration of anesthesia has contributed in no small way to the saving of babies' lives in a fair number of cases.

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DISCUSSION

DR. GEORGE KAMPERMAN, Detroit, Mich. (by invitation).—In general the application of pain-relieving drugs in obstetrics has been a definite advance, but a final solution has not yet been reached. The aim of these methods in obstetrics has been to relieve or diminish the pain of labor, and this aim has been accomplished to a great extent. This has had a favorable psychic effect on the patients, and they no

longer tell of the harrowing details of labor to frighten their expectant friends. And the patient who has had one baby with little pain stands in no great fear of the next labor.

Another and unexpected advantage has been an apparent shortening of the first stage of labor. While we can never say what would have happened without analgesia in a given case, yet the more rapid progress after giving analgesia is so often noted that it does seem more than a coincidence.

One must, however, face the fact that the giving of pain-relieving drugs creates new problems. The lack of coordination of the patient under the influence of pain-relieving drugs often causes a slowing down of the progress of the second stage of labor. This results in an increased incidence of interference. Furthermore, a restlessness often develops which may cause one to despair of being able to conduct the delivery in an orderly and aseptic manner. About the only solution of this problem is an anesthetic and an operative termination of labor. This may present no new problem for the obstetrician who delivers all patients by operative means after the first stage of labor is ended, but to those who like to allow their patients to deliver spontaneously, it means a definite change in procedure. We cannot believe, as Dr. Bill states, that this is entirely a choice of the obstetrician. We do agree with the essayist that with the use of pain-relieving drugs one can be freer to wait until interference is of the minor type.

Furthermore, there are certain special dangers and special management and selection are necessary to avoid these. Irving has called attention to the fact that pneumonia is a possible complication if the patient has an upper respiratory infection, which is in accord with our experience. The lessening of reflexes also makes aspiration of vomitus a danger. Prolonged labors may be accompanied by a dehydration which may require active treatment.

In general, we have felt that pain-relieving drugs had no untoward effect on the babies. It is true that the babies are often listless and require definitely more resuscitation to establish respiration and a healthy, vigorous cry.

Our complacency in this matter was somewhat shaken recently by the work of Schreiber of Detroit. Schreiber bases his opinions on Courville's brain findings in cases of death following nitrous oxide anesthesia, and on his own findings in cases of death due to industrial gases. In cases with cyanosis an anoxemia may cause a focal necrosis of brain cells, which if not fatal will later result in spastic muscles or in mental deficiencies. Schreiber bases his assumptions in regard to analgesia on a series of babies with spastic muscles, which he believes have had brain cell necrosis caused by cyanosis. While Schreiber's work is not conclusive and not entirely convincing, he has pointed out the existence of a possible danger where we thought none existed. His work has caused us at Harper Hospital to give more careful consideration to dosage.

We are not in accord with Dr. Bill that the aim should be to have a completely painless labor. We believe the labor should be allowed to progress for some time and that the drug should be given only when the pain becomes definitely annoying. We also feel that our patients need not be kept so deeply under the influence of the drug as was at first our practice. With a smaller dosage the patients may complain of distress, but be completely forgetful of it after the labor is over.

In general, we feel that to conduct labors safely with analgesia requires the best of hospital facilities. The new problems created tax the resources of even the better trained obstetricians. The greatest danger is that many of these procedures may be practiced by men who have not the facilities or the skill to meet all the problems. When we advocate something that is safe in expert hands, we must not forget that the general practitioner is still the obstetrician for the masses. In less skilled hands the pain-relieving drugs may add to maternal mortality and morbidity.

DR. G. D. ROYSTON, ST. LOUIS, MO.—In the last 20,000 deliveries in the Washington University Clinic, a majority of the patients have received scopolamine or hyoscine in various combinations. The substitution of barbiturates for opiates has broadened the scope of its use and given increased satisfaction.

We agree with Dr. Bill's indications for painless labor, feeling that much premature interference is avoided, when the obstetrician is spared the importunities of the patient. We disagree with him in limiting hyoscine to primiparas. In our clinic, whenever we consider the patient is definitely in labor and complaining of pain, regardless of parity, analgesia in some form is administered. Ward patients must have 2½ to 3 fingers dilatation before receiving hyoscine. During the prodromal stages, often barbiturates alone are given. Ordinarily hyoscine in ampule form is injected with 1/6 gr. or less of morphine sulphate. Barbiturates may be substituted for opiates. The desired degree of seminarcosis is maintained by repeated doses of hyoscine, properly spaced, and is determined by the patient's locomotor coordination, dilatation of pupils, etc. This is continued until delivery actually occurs. The method of delivery is more optional with the obstetrician than a matter of necessity. The opiate, if any, is never repeated after the initial dose.

Animal and clinical studies convince us that fetal respiratory difficulties may follow the administration of opiates given late in labor. Hyoscine in the doses used has little or no effect on respiration. The effects produced on respiration by morphine are twofold, the one directly on the respiratory center, the other on the constricting muscles of the bronchiole.

We disapprove of inhalation anesthetics during the first stage of labor, except for the occasional case, and we limit nitrous oxide to the late second stage of labor. Ether or chloroform on the open mask is used during the actual delivery when there are no contraindications from the cardiac, pulmonary, or toxemic point of view. Ether is regularly used for repair. An interne and a nurse remain constantly with every patient under seminarcosis. Probably 10 per cent to 20 per cent of such patients are restless and require restraint, yet have perfect amnesia. This restlessness and the need of constant attendance of trained help are the only disadvantages of the method as we use it.

We feel that morphine-hyoscine modified with barbiturates is the most valuable method of seminarcosis available. It can be safely and profitably used by any one who thoroughly understands the action of these drugs. The earlier reports which have stressed increased fetal asphyxia have been chiefly due to improper use of the method and too much general anesthetic at the time of delivery. Fetal asphyxia occurs without analgesic methods and the increased asphyxia that results from such methods is minimal, it having no effect upon fetal mortality as our reports in the past have repeatedly shown.

DR. WILLIAM A. SCOTT, TORONTO, CANADA.—The alleviation of pain in the first stage of labor is one thing, the routine attempt to produce painless childbirth is another. It is undoubtedly true that the skilled obstetrician working with a skilled anesthetist, under the most perfect circumstances and surroundings, can without any great difficulty and with a high degree of success get painless childbirth. It is to be remembered, however, that if he does this, and more particularly if he teaches it, the general practitioner without his skill and without ideal surroundings will be forced to attempt the same procedure.

I know no method of painless childbirth that does not in a fair percentage of cases lead to great restlessness. With unfavorable surroundings one of two things must follow, either complete anesthetization of the patient and instrumental delivery, or else a deepening of that drug narcosis which we know is not free from danger. More than that, one finds that if the obstetrician, who is anxious to succeed in producing a painless labor, finds that his method is not going smoothly, then

inevitably some type of operative delivery follows. I feel, therefore, that this Society should give some note of warning against a routine method of trying to produce painless childbirth.

DR. COLLIN FOULKROD, PHILADELPHIA, PA.—Any procedure reported from this Society is going to be applied by the great majority of men who have graduated within the past five years. It is very unwise to allow those men without experience to use these drugs, on the word of a man, who has had 2,000 or more cases, that he can conduct labor successfully with them.

Women often insist upon amnesia, but we should sift out the patients who can be properly treated in this way. The doctor must, however, carry her through with the least possible damage to herself and the baby. Amnesia certainly reduces the mental control which is needed in the latter half of labor. Following this method universally will lead to disaster.

A personal selection of the drug is essential. Some women become excited. Some will immediately relax the cervix by the use of sodium amytal, while in others it will have no effect on the cervix. Long before this method was instituted Dr. Newell read a paper which embodied the same ideas and which some of us still carry out, but based upon morphine and scopolamine.

If you will encourage your patients to go on to two fingers dilatation you will have them come through the labor without any serious remembrance of the difficulties of labor in normal cases. There is no question that sodium amytal is beneficial in many deliveries. I merely suggest that patients should be classified, and that if they want analgesia they should go to a skilled obstetrician and not to a general practitioner.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—In 1915 when Dr. John Polak came back from the Krönig and Gaus Clinic in Germany, he brought with him the technique of "Dämmerschlaf" or "twilight sleep," i.e., morphine and scopolamine analgesia and amnesia. From an experience extending over these twenty years, it is still the analgesic of choice so far as I am concerned. Furthermore morphine-scopolamine is the safest drug for the general practitioner to use.

Cyclopropane anesthesia is to be recommended for your serious consideration. It requires 80 to 90 per cent of oxygen to be given with it, and therefore with this amount of oxygen the baby is never asphyxiated.

In all of these methods under discussion, the man who is giving the analgesia after all holds the balance of success or failure in his hands. If he has had enough experience and his judgment is sufficiently sound he can take any of these drugs and produce satisfactory results with them.

DR. CARL H. DAVIS, WILMINGTON, DEL.—Various clinics have developed plans for pain-relief which work for the average patient. Most of us will agree, however, that the obstetrician should be familiar with all methods and adapt the procedure to the problems presented by the individual patient rather than attempt to adapt the patient to a particular method of pain-relief.

The general plan which I have employed for a great many years has been to use hyoscine and heroin for the first stage of labor and nitrous oxide analgesia for the second stage. This is satisfactory for the majority of patients. Occasionally I have used rectal ether because I wished to secure a slowing up of labor over a considerable period of time for a patient who had a slowly dilating type of cervix. During the last few years I have used barbiturates somewhat as a first stage procedure. The woman who comes to the hospital with beginning but not active labor, will have sufficient discomfort to keep her from sleeping. A dose of 6 gr. of sodium amytal will be sufficient to give that woman a few hours of satisfactory rest. I follow this with heroin and hyoscine analgesia in the first stage of labor, and then give intermittently a nonexplosive type of inhalation gas in the second stage.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—The combination of morphine and atropine is a tried and old combination. The atropine undoubtedly enhances the effect of the morphine and in the rigid cervix has a remarkable effect in relaxing it. Dr. Davis' mention of heroin is of interest. To most of us that drug is unavailable for it is banned in New York State.

DR. BILL (closing).—I wish further to emphasize the point that we must not adhere to any one method but rather use a combination of several methods adapted for the individual patient. We must consider the safety of the baby primarily. In the series of cases reported which had no fetal mortality (corrected) the analgesia evidently had no ill effects. Blood studies of cases in which gas and ether anesthesia were used showed no anoxemia. In starting the analgesia we do not wait for 2 or 3 fingers dilatation but give medication or inhalation analgesia as soon as the patient complains of pain.

In comment upon the argument that such procedures as these are not safe in the hands of the general practitioner, I think that we must stop lowering our standards to the level of the untrained man and must begin to think of training men to do the things which we consider ideal.

THE CONSERVATIVE TREATMENT OF PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA*

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THE maternal death rate in premature separation of the normally implanted placenta is increased if the hemorrhage is internal; that is, retained within the uterine cavity, or if there coexists a toxic state, such as preeclampsia, eclampsia, or nephritis. From Jan. 1, 1916 to April 1, 1937, 353 patients with premature separation were admitted to the Boston Lying-in Hospital, all beyond twenty-eight weeks of pregnancy. Table I shows the relative distribution of deaths depending upon these two factors. It is evident that retention of blood within the uterus was more often associated with a fatal outcome than was the presence of toxemia. Therefore these 353 cases are divided into two groups: those with external hemorrhage and those with internal hemorrhage.

EXTERNAL HEMORRHAGE

There were 234 cases in this group. Since this report concerns only methods of treatment and their results, no other aspects of premature separation will be considered. In Table II are given the maternal mortalities following simple pelvic delivery, complicated pelvic delivery, and cesarean section. One notes in the 170 patients delivered normally, by low forceps or by the breech, in every instance only after full cervical

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dilatation, that there were no deaths. Labor was allowed to progress without interference. If bleeding occurred before the onset of labor, contractions were induced in some instances by rupture of the membranes or by metreurysis. Of the total 204 cases delivered through the pelvis, 5 or 2.4 per cent received transfusions, as did an equal number, or 16.7 per cent of the 30 cesarean sections. The increased frequency of transfusion among the cesarean sections indicates a greater blood loss than was the case with those women delivered through the pelvis.

TABLE I. THE RÔLE OF INTERNAL HEMORRHAGE AND TOXEMIA IN DETERMINING MORTALITY

	CASES	DEATHS	PER CENT MORTALITY
No toxemia	224	8	3.5
Toxemia	129	10	7.7
External hemorrhage	234	4	1.7
Internal hemorrhage	119	14	11.8

TABLE II. EXTERNAL HEMORRHAGE. BOSTON LYING-IN HOSPITAL. MATERNAL MORTALITY ACCORDING TO THE METHOD OF DELIVERY

	CASES	DEATHS	PER CENT MORTALITY
Normal delivery, low forceps, breech	170	0	0.0
Pelvic operative delivery	34	3	8.8
Cesarean section	30	1	3.3

TABLE III. EXTERNAL HEMORRHAGE. FETAL MORTALITY

	PELVIC DELIVERY 207 INFANTS (INCLUDING 3 PAIRS OF TWINS)		CESAREAN SECTION 30 INFANTS	
	NO.	P.C.	NO.	P.C.
1. Dead on admission	29	14.0	5	16.7
2. Under 4 pounds	32	15.4	6	20.0
3. Stillborn	45	21.2	7	23.3
4. Died after birth	27	13.0	4	13.3
5. Gross mortality (3) + (4)	72	34.7	11	36.7
6. Not dead on admission or under 4 pounds	146		19	
7. Net fetal mortality (6)	11	7.5	0	00.0

Of the 237 infants in this group, including 3 pairs of twins, 34 or 14.3 per cent were dead *in utero* when their mothers were admitted to the hospital. Moreover, 40 others, or 16.8 per cent, although alive *in utero,* were under 4 pounds in weight when born. In almost one-third of the cases, therefore, salvage of the infants was either impossible or unlikely. In assigning proper values in fetal mortality to methods of treatment, the net death rate, which applies only to those infants alive on admission and over 4 pounds, is of more importance than the gross death rate, which embraces all infants, regardless of their vital condition or size.

Among the infants delivered through the pelvis the net fetal mortality was 7.5 per cent, while with cesarean section it was zero. The gross mortality in both instances was about the same being 34.7 per cent in pelvic delivery and 36.7 per cent in cesarean section (Table III).

INTERNAL HEMORRHAGE

In this class are all cases where the bulk of the hemorrhage was retained within the uterus. Bleeding which is entirely concealed is the exception, since in all but 2 of our 119 cases of internal hemorrhage, there was some visible bleeding at some time. Internal hemorrhage has also been described as *ablatio placentae* or *abruptio placentae* according to which appellation most suits the fancy. This type of case is often accompanied by the so-called uteroplacental apoplexy, although unless one inspects the uterus either at operation or at autopsy, no one may know which patients present this anatomic picture and which do not, since there are no characteristic physical signs denoting the infiltration of the myometrium with blood and serum.

TABLE IV. INTERNAL HEMORRHAGE. FETAL MORTALITY

	PELVIC OPERATIVE DELIVERY 16 INFANTS		CESAREAN SECTION 70 INFANTS (1 PAIR TWINS)		CONSERVATIVE TREATMENT 34	
	NO.	P.C.	NO.	P.C.	NO.	P.C.
1. Dead on admission	12	75.0	33	47.1	25	73.5
2. Under 4 pounds	2	12.5	3	4.3	2	5.8
3. Stillborn	13	81.2	39	55.7	29	85.3
4. Neonatal deaths	2	12.5	4	5.7	1	2.9
5. Gross mortality (3) + (4)	15	93.7	43	61.4	30	88.1
6. Not dead on admission or under 4 pounds	2		34		7	
7. Net mortality (6)	1	50.0	7	20.6	3	42.8

At this point it may be well to consider the fetal mortality in internal hemorrhage. Seventy, or 58.3 per cent, of 120 infants were dead on admission and 7, or 5.8 per cent, were under 4 pounds. In about two-thirds of the cases, therefore, there was little or no chance of saving the baby. The net fetal mortality with pelvic operative delivery was 50.0 per cent, and the gross 93.7. With cesarean section, the net fetal mortality was 20.6 per cent, while the gross was 61.4 per cent. Under conservative treatment, the net mortality was 42.8 per cent and the gross was 88.1 per cent. (Table IV). As regards the infant, if it be alive, the advantage is with cesarean section; not so is this the case as regards the mother, as I shall demonstrate.

For at least twenty years the method of controlling the hemorrhage approved by most American obstetricians has been by cesarean section. Table V indicates that the results have been far from good. An average mortality rate of 20.5 per cent is many times that of placenta previa;

TABLE V. INTERNAL HEMORRHAGE. RESULTS WITH CESAREAN SECTION AS REPORTED BY VARIOUS AUTHORS

AUTHOR	CASES	DIED	PER CENT
Willson[1]	21	4	19.0
Brodhead[2]	8	3	37.4
Williams[3]	10	3	30.0
Fitzgibbon[4]	4	1	25.0
Davis and McGie[5]	29	4	13.8
Siegel[6]	11	2	18.2
	83	17	20.5

indeed there is no other fairly frequent complication of pregnancy, with the possible exception of eclampsia, that has been so often fatal. The woman with this form of internal hemorrhage is not only handicapped by acute blood loss, but she is also often the victim of shock caused by sudden distention of the uterus. In three-fifths of the cases toxemia is present, on occasions accompanied by partial or complete suppression of urine. It would be difficult to envisage a more dangerous basis for such a surgical operation as cesarean section, a procedure in itself of considerable magnitude and often complicated by further hemorrhage. All judgment should be against it, provided there exists a safer and less radical means of escape.

Such a solution of the difficulty was brought to the attention of American obstetricians in 1931 by the late John Osborn Polak.[7] He reported 16 cases of internal hemorrhage treated by rupture of the membranes, the insertion of a tight cervical and vaginal pack and the application of a Spanish windlass abdominal binder. This treatment was based upon the method in use at the Rotunda Hospital in Dublin. Only one of Polak's patients died, giving a mortality of 6.2 per cent. Discouraged by our results with cesarean section in these cases at the Boston Lying-In Hospital, we began the use of Polak's method, and in 1934 I reported before the New York Obstetrical Society an equal number of cases, also with one death, and thus accompanied by the same mortality. In 1936, Heffernan[8] of Boston recorded 7 cases with no deaths.

It has been stated that since the uterus is often infiltrated with blood and serum it is paralyzed, and therefore it cannot expel its contents. In only one case in our series of 34 patients treated conservatively did this occur; the remaining 33 delivered themselves normally or by low forceps. The only fatality occurred in this woman who entered with jaundice, a severe toxemia and suppression of urine, and died undelivered. It is beyond probability that cesarean section would have saved her life. Fear has also been expressed, for the same reason, that the uterus would fail to contract following delivery, and that the patient would succumb to postpartum hemorrhage. Our experience has been that the uterus has behaved well. In only one instance was it necessary to resort to tamponade. The most remarkable argument advanced by

the proponents of cesarean section is that it affords an opportunity to perform a hysterectomy. Table VI shows the results in 33 Porro operations appearing in the literature. The logic is not apparent which impels one to perform an operation with a 20 per cent mortality, so that he may convert it into another with twice the death rate. We have in the past performed 6 Porro operations in this type of case with 3 deaths, a mortality of 50 per cent.

TABLE VI. INTERNAL HEMORRHAGE. RESULTS WITH PORRO CESAREAN SECTION AS REPORTED BY VARIOUS AUTHORS

AUTHOR	CASES	DEATHS	PER CENT
Welz[9]	3	1	33.3
Willson	21	10	47.6
Davis and McGie	6	0	00.0
Fitzgibbon	3	2	66.7
	33	13	39.4

TABLE VII. INTERNAL HEMORRHAGE. BOSTON LYING-IN HOSPITAL. MATERNAL MORTALITY ACCORDING TO THE METHOD OF DELIVERY

	CASES	DEATHS	PER CENT MORTALITY
Pelvic operative delivery	16	3	18.7
Cesarean section	69	10	14.5
Conservative measures	34	1	2.9

Among the 69 cases of internal hemorrhage subjected to cesarean section 19, or 27.5 per cent, required transfusion, as contrasted with 4, or 11.7 per cent, of the 34 delivered by conservative measures.

Since 1931 no patient with internal hemorrhage has been delivered by cesarean section unless the infant was living and viable and the mother in good condition (Table VII). Twenty-six patients have been treated by the pack and Spanish windlass, with the one death already noted, and 8 others who entered in active labor have been left alone, with the exception of one case in which the membranes were ruptured artificially.

Our death rate for conservative treatment has been 2.9 per cent, as against 14.5 per cent for cesarean in 69 cases of the same type, or a lowering of our mortality to one-fifth of its former figure.

SUMMARY

1. Three hundred and fifty-three cases of premature separation of the placenta are reported; of these, 234 had external and 119 internal hemorrhage.

2. In 170 patients with external hemorrhage delivered through the pelvis by simple means there were no deaths.

3. In 30 cases of external hemorrhage treated by cesarean section, the death rate was 3.3 per cent.

4. In 69 cases of internal hemorrhage delivered by cesarean section the death rate was 14.5 per cent.

5. In 34 cases of internal hemorrhage treated by conservative measures the mortality was 2.9 per cent.

6. Conservative measures give a better prognosis for the mother in both types of premature separation of the placenta.

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DISCUSSION

DR. WILLIAM E. STUDDIFORD, JR., New York, N. Y. (by invitation).—I fully agree that Dr. Irving's first group, which consists of those with partial placental separation, should be treated conservatively. It was a little surprising to note the large number of these cases formerly treated by cesarean section. The slight degree of placental separation present in most of these patients is evident by the fact that 19 living infants were obtained in these operations. The fetal death rate is probably increased by allowing these patients to deliver spontaneously, since the degree of placental separation may increase during the process. The maternal death rate should not be much above normal expectation. On the other hand cesarean section must inevitably lead to greater maternal risks.

The second group includes the severe type of case which is often characterized by complete placental separation and by hemorrhagic infiltration of the myometrium. While it has always seemed best to allow these patients to deliver spontaneously if possible, certain cases present such obstacles to rapid delivery that it has always seemed to me that they were best handled by cesarean section. Occasionally, due to a functionless myometrium, hysterectomy even may be indicated. It is a little startling to hear that cesarean section can be abandoned as a method of treatment in these patients.

Cesarean section with or without hysterectomy is performed, as a rule, only on the most severe cases. The mortality in this small group is of course high. It is hardly fair then to compare the cesarean section mortality based on this group with the general mortality for all degrees of placental separation.

I have had no experience with the vaginal pack and Spanish windlass. However, it might be of interest for the sake of comparison to review the results of treatment in these cases at Bellevue Hospital.

From May 1, 1934 to March 1, 1937 approximately 5,000 deliveries occurred. In this group were present 60 cases of premature separation of the placenta after the twenty-eighth week of pregnancy. Sixteen showed some evidence of toxemia. Trauma as an etiologic factor occurred once. Forty-two cases were examples of external hemorrhage, while 18 were classified as internal hemorrhage.

With only one exception all the cases of external hemorrhage were delivered pelvically. In addition 11 cases of internal hemorrhage were delivered by this route. Hemorrhage was treated by rupture of the membranes, by the occasional use of the hydrostatic bag and by transfusion. The latter procedure was utilized in 26 per cent of the patients. Out of a possible 53, 25 infants were discharged in good

condition, a mortality of 55 per cent. The remainder succumbed to the causes described by Dr. Irving. There was one maternal death, a toxic patient with concealed hemorrhage and bacterial endocarditis, who succumbed four days postpartum from cardiac failure.

In only one instance did hemorrhage occur after the third stage. Again this was a patient with concealed hemorrhage and complete separation. Because bleeding could not be controlled with packing postpartum, a hysterectomy was performed, hemorrhagic infiltration of the uterus being present. One patient with external hemorrhage was delivered by cesarean section, but additional indications for the operation were present in this case.

In seven patients it was felt that the situation could best be handled by cesarean section. All of these were instances of complete separation with a dead fetus. Transfusion was used in all cases and was often repeated. In two cases the uterus did not react after the removal of the fetus and placenta and a hysterectomy was performed. There was one maternal death, which occurred fourteen days postpartum from staphylococcus sepsis in a patient treated by cesarean and hysterectomy. This patient received 3,100 c.c. of blood before and after operation.

The maternal mortality in the group treated by cesarean section amounted to 12.5 per cent; in the group delivered pelvically to 1.9 per cent; in the group as a whole to 3.3 per cent.

DR. NORRIS W. VAUX, PHILADELPHIA, PA.—My experience has led me to separate all the cases of suspected premature separation into the following groups:

1. Those cases with mild frank bleeding, whose general condition and that of the infant in utero has not yet become affected by blood loss.

2. Those cases which undoubtedly have concealed or frank hemorrhage sufficient to produce shock and collapse from blood loss. This is frequently seen in emergency cases, when the placenta has become completely detached and intrauterine fetal suffocation has occurred.

The first group should be treated conservatively, for a time at least. In the second group the immediate treatment should be directed towards combating the shock and collapse, followed by prompt radical intervention.

In the last two years at the Philadelphia Lying-In Hospital, we have felt that the proved cases of premature separation should be treated by immediate intervention by cesarean section, preferably under local anesthesia. This is directly the opposite of the methods of conservatism advocated by Dr. Irving. It has been our custom, however, to use conservatism in the cases of mild or partial separation which evidence no results of excessive blood loss, but these individuals must be kept under constant observation, and the more radical methods employed if evidence of further separation presents itself.

It is not appropriate to compare the conservative and radical policies on total groups of cases. The underlying etiologic factors, such as toxemia and associated conditions, must necessarily influence the method chosen and these affect the figures for certain methods of therapy.

As to the question of removal of the uterus after cesarean section, Dr. Irving has pointed out the added risk associated with hysterectomy, and I most heartily agree. Very rarely is this procedure justified, as the recuperative powers present in the uterine musculature are remarkable.

DR. K. DE SNOO, UTRECHT, HOLLAND.—During a period of thirty years I have observed as many as 228 cases of premature separation of the placenta. In 127 cases more than half of the placenta was separated, in 101 less than a half. Most of these latter cases were diagnosed only after birth by the finding of clots on the maternal side of the placenta. The first group, on the other hand, forms the severe cases, generally accompanied by the classic symptoms.

In the first five years my treatment was active, including such procedures as podalic version, Braxton Hicks and dilatation of the cervix. For twenty-six years, however, the treatment has been wholly expectant.

RESULTS OF THE TREATMENT OF PREMATURE SEPARATION OF THE PLACENTA IN 228 CASES

	COMPLETE SEPARATION		PARTIAL SEPARATION	
	11		3	
Rotterdam 1907-1910	Mothers dead	2	Mothers dead	0
(Active treatment)	Children dead	11	Children dead	1
	72		53	
Rotterdam 1911-1926	Mothers dead	7	Mothers dead	0
(Conservative treatment)	Children dead	72	Children dead	20
	44		45	
Utrecht 1927-1936	Mothers dead	4	Mothers dead	0
(Conservative treatment)	Children dead	44	Children dead	30

This table shows the results for mother and child. The infant mortality in total separation is 100 per cent, in partial separation 50 per cent. By conservative treatment not one of the mothers with partial separation died, while of the mothers with complete separation 11 of 116 or 10 per cent died. The conservative method of treatment is morphine, and when necessary stimulants and blood transfusion.

Delivery after complete separation was accomplished one hundred times spontaneously, ten times artificially. Of the 11 women who died, 6 died before parturition, 5 from hemorrhage, 1 from uremia; and 5 after parturition, 2 from anuria, 1 after vaginal cesarean section, and 2 from hemorrhage postpartum after artificial delivery. Not a single patient bled to death after spontaneous delivery.

Regarding the causes of the premature separation: we find the frequency in normal women to be 1:22,000; in toxemia and nephritis, 1:220; in eclampsia, 1:57. There was no difference between the cases of complete and partial separation in respect to the albuminuria, the hypertension, and even the future prognosis. For out of 101 women with partial separation, 4 died more than one year after the separation from chronic nephritis or apoplexy, while out of 127 women with complete separation, 6 died. This proves that the cause of retroplacental hemorrhage lies in the vessels, and that it is accidental whether the hemorrhage is slight or considerable. On the other hand it is striking to see that all women with partial separation have recovered, while those with considerable separations have shown very severe disturbances, especially of the kidneys, and that 3 have died from anuria. Thus it is evident that the separation is not the result of the impaired kidneys but that these serious symptoms develop through the large retroplacental hemorrhages.

In my opinion the whole process develops as follows: From the products of gestation, spasms of the vessels arise with disturbed circulation. This defective circulation brings about, with the aid of the hypertension, hemorrhages in different organs and in the decidua. When arterial sinuses are opened, a severe hemorrhage may occur, accompanied by separation of the placenta and distention of the uterus. This distention may produce rents in the peritoneum and hemorrhages in the muscle. By this rapid distention furthermore, reflex spasms of the vessels occur. This reflex spasm causes the anuria, with eventual necrosis of the kidney cortex and bleeding and necrosis of the liver. In short the symptoms are the same as develop after eclamptic convulsions. These disturbances are, it is true, much more frequent in eclampsia than in the severe forms of premature separation, but this is due to the susceptibility of the tissues to disturbances in the circulation. This, in general, is less in premature separation than in eclampsia.

DR. RUDOLPH W. HOLMES, CHICAGO, ILL.—Spiegelberg over seventy-five years ago clearly demonstrated that not rarely (about 1 in 200 deliveries) inspection of the placenta postpartum reveals flecks of blood, up to the size of a goose's egg, of a dirty putty-like appearance, which are clots in which the hemoglobin has been destroyed. These produce no clinical signs, or at most trivial symptoms which are not recognized. From such insignificant entities we run the gamut of every degree of placental separation up to complete ablation, and every degree of hemorrhage up to those obstetric cataclysms, ushered in by profound hemorrhage or those severe cases of *Couvellaire apoplexy.* In both these types there may be not one drop of blood escaping from the vagina.

I have never conceded that those cases of ablatio without external bleeding carry a higher mortality rate for mother and baby than the open type. The only difference lies in the fact that the diagnosis is delayed in instances of *absolute concealment.* On the other hand, in the open hemorrhages, the amount of blood which escapes is never the criterion of the amount which has left the circulation. I firmly believe that we should divide all instances of ablatio into *absolute concealment* and *relative concealment.* I have tabulated all the symptoms which are reputed to occur with ablatio placentae. Each and every sign and symptom so recognized prevails with equal frequency in the occult and overt types, except that external bleeding is constant in the latter.

If we concede for the moment that absolute concealment does carry an inherent jeopardy wanting in the relative types, then we should concede that the tampon is entirely contraindicated for it immediately converts the open into a concealed type. But, we know that for over 150 years the Dublin School has employed the tampon for "accidental hemorrhage" with signal success. I heartily substantiate Dr. Irving's stand in the use of the tampon in selected cases. I would also raise my protest with that of Dr. Irving that a routine cesarean section for all instances of ablatio is inexcusable.

In my personal experience of 26 instances of severe clinical ablatio placentae, I have found that the hemorrhage and uterine changes produce with rare exceptions a marked cervical relaxation, a dilatable os. I voice this view with great timidity in view of the present reaction to manual dilatation, but I feel that most ablatios may be delivered by manual dilatation and version (vel forceps or craniotomy) far more quickly than is possible in waiting for the "set up" and then performing a cesarean section.

DR. IRVING (closing).—Of the 119 cases I reported that fall into the internal hemorrhage group, some had complete separation and some did not. It is not always possible to tell whether the separation is complete or whether it is partial.

The 119 cases fell, however, into the same group as those discussed by Dr. Studdiford and Dr. Vaux. We felt just as they did until we abandoned cesarean section in 1931. Our conversion to conservative measures was due to the 16 cases of Dr. Polak. This method lacks rapidity but I am not willing to admit that it is less safe than cesarean section. In our own hands it has been much safer.

I would like, to take exception to Dr. Holmes' statements regarding manual dilatation. That method has been anathema to me ever since I was an interne and I have taught that it is one of the most fatal maneuvers in obstetrics.

THE ETIOLOGY OF CONGENITAL MALFORMATIONS IN THE LIGHT OF BIOLOGIC STATISTICS*

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IT IS said that development results from the interaction between inherited tendencies contained within the egg substance itself, and the external conditions which surround and act upon this substance (Stockard).[1]

It is common knowledge that many congenital abnormalities are inherited. The question arises, however, as to whether all defects have their origin in this manner, or whether some of them may be due to disturbances within the environment of the otherwise normal ovum.

A number of observations support the idea that man can influence the environment of the ovum sufficiently to modify its growth. Stockard[1] subjected the eggs of fish, during early stages of development, to the action of weak solutions of alcohol. The resulting embryos exhibited marked abnormalities in the structure of the central nervous system and organs of special sense. Bagg[2] likewise modified the growth of the eye and brain of rat embryos by exposing them to radium irradiation. Murphy[3] assembled evidence that radium and roentgen exposure will arrest the growth of the human embryo, microcephaly being the most common sequel.

With respect to spontaneously occurring malformations, Mall[4] found a high incidence of abnormalities among aborted, human embryos, and ones from tubal gestations. The very large number of pathologic embryos found in the tubal pregnancies was one of the strongest arguments to him that they were not the result of germinal influences, but due to unsuitable external conditions.

It is conceivable, however, that the pathologic embryos examined by Mall, may have acquired their unusual maternal relationships as a result of abnormal germinal characteristics. In such an event, the ensuing maldevelopment would have been due primarily to hereditary causes.

It is generally agreed, therefore, that many congenital malformations are inherited, also that the development of the ovum can be modified under experimental conditions. The evidence does not appear to be entirely convincing, however, that spontaneously occurring abnormalities can be due to environmental factors. The present report deals with certain characteristics of a series of families possessing congenitally

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malformed children. These are presented in order to show the apparent influence, and relative importance, of heredity and environment as factors in the production of congenital defects in man.

MATERIALS AND METHODS

The material forming the basis for the study was secured in the following manner:

There were found in the files of the Bureau of Vital Statistics, Department of Health of the State of Pennsylvania, 130,132 death certificates for stillborn and liveborn individuals who died in Philadelphia during the five years between Jan. 1, 1929, and Dec. 31, 1933. Each of these certificates was examined and among them were found 1,476 cases of congenital defect.

The deceased individual was considered to have possessed an abnormality under either of two conditions: (1) if the malformation involved the surface of the body, or, (2) if internal, its presence had been disclosed by operation or necropsy. Diagnoses not conforming to these requirements were considered as not verified and were excluded from further consideration. This procedure gave 890 cases for study. An attempt was made to interview the mother of each individual, the visits being carried out in the summer of 1934, by three fourth-year medical students. By this means, forty-five additional malformed brothers and sisters of the defective offspring were located, giving information upon a total of 935 defective individuals. Since approximately 80 per cent of the deformed persons were born in hospitals, these institutions were visited, and pertinent facts were extracted from their records.

THE DATA

The location of the *chief* malformation of each individual by body system is recorded in Table I. The diagnoses of the largest single group appearing in Table I, are given in Table II. The seriousness of the defects is indicated by the fact that 90 per cent of the individuals died within a year of birth.

The familial characteristics having a possible bearing upon the etiology of the physical abnormalities are considered under two headings: (A) environment and (B) heredity.

(A) ENVIRONMENT

The frequency with which certain of the environmental characteristics occurred is given in Table III. In this table, the term "chronic illness" refers to sickness which existed at the time that the malformed child was conceived. The Wassermann reactions are those which were taken when the mothers were pregnant with their malformed offspring.

Pelvic disease relates to any pelvic condition for which the mother received treatment prior to the conception of her defective child. Preconceptional douching deals with the use of contraceptive chemical douches employed at the time that the malformed child was conceived. Although no control data were available, the attributes in Table III did not appear to occur unusually often.

TABLE I. CLASSIFICATION OF CHIEF DIAGNOSES BY BODY SYSTEM

Showing the location of one malformation for each defective individual, arranged according to body system. In case two or more defects were present, the most serious one was selected. Note the great frequency of malformations involving the nervous system.

BODY SYSTEM	INDIVIDUALS	
	NUMBER	PER CENT
Reported	935	100.0
Nervous	566	60.5
Gastrointestinal	140	15.0
Bones, muscles, skin	103	11.0
Cardiovascular	80	8.6
Monsters not described	28	3.0
Genitourinary	10	1.1
Ill-defined	4	0.4
Respiratory	3	0.3
Unstated	1	0.1

TABLE II. NERVOUS SYSTEM DIAGNOSES

Showing the nervous system defects according to diagnosis. Note the seriousness of the malformations, and the great frequency of hydrocephalus and spina bifida.

DIAGNOSIS	INDIVIDUALS	
	NUMBER	PER CENT
Reported	566	100.0
Hydrocephalus alone	180	31.8
Spina bifida alone	112	19.8
Anencephalus	98	17.3
Hydrocephalus with spina bifida	93	16.5
Meningocele	26	4.6
Craniorachischisis	25	4.4
Microcephalus	13	2.3
Encephalocele	8	1.4
Mongolism	8	1.4
Others	3	0.5

TABLE III. FAMILIAL CHARACTERISTICS RELATING TO ENVIRONMENT

Showing the frequency with which some of the familial characteristics relating to environment as a possible etiologic factor, were observed. Note the relative infrequency of these attributes.

CHARACTERISTIC	FAMILIES STUDIED NUMBER	CHARACTERISTIC PRESENT PER CENT
Chronic illness of Father	569	9.3
Chronic illness of Mother	640	8.8
Positive maternal Wassermann	324	12.4
Previous maternal pelvic disease	628	10.8
Previous atypical menstruation	654	12.5
Preconceptional douching	345	25.5

Frequency of Reproduction.—Two hundred and eight families each had two or more children born before the birth of the congenitally malformed child.[5] Reproduction occurred in this group no more frequently than in a series of control families having normally developed offspring.

Month of Conception.—The month of conception of 935 malformed individuals was studied.[6] The greatest frequency of these conceptions occurred in the summer months. This was contrary to the findings of Petersen,[7] who observed the greatest incidence in the winter and spring months. These findings indicate that there is no unusual seasonal occurrence in the time of conception of congenitally malformed individuals.

Diet.—The diet of 545 mothers was investigated. The important foods, such as milk, leafy vegetables, fruits, and whole grain breads were not used by these mothers in amounts sufficient to meet the mineral and vitamin standards, as generally recommended for pregnant women. The most obvious dietary deficiencies were in calcium, phosphorus, iron and vitamins B and C. Accurate control figures for these observations, however, were not available.

Coincidence of Malformation with Placenta Previa.—Placenta previa occurred only once in 741 malformation pregnancies. Its frequency in the general population, according to Williams,[8] is about one in 1,000 cases in private practice. It is possible that no additional instances of placenta previa would have been met had 1,000 malformation pregnancies been studied.

(B) HEREDITY

Color.—There were 814 white and 76 negro, malformed individuals. These figures gave a ratio of 5.72 malformed whites per 1,000 white livebirths, and 3.17 malformed negroes per 1,000 negro livebirths occurring in Philadelphia during the five-year period in question. The rate for the whites, therefore, was nearly twice that for the colored. This racial selectivity of malformations is borne out by governmental statistics.[9]

Maternal Age.—Data dealing with the ages of 570 mothers at the births of 607 malformed children, and 1,583 normally developed siblings were available for analysis.[10] The proportion of defective to normal offspring at different maternal ages was found to be as follows: (a) lowest when the mothers were between twenty and twenty-five years of age; (b) more or less constant when the mothers were between fifteen and thirty years of age; (c) increasing from year to year when the mother had passed thirty; (d) greatest after the mothers had passed forty years of age, at which time the ratio of defective to normally developed children was approximately three or more times that noted before the mothers were thirty years old.

Birth Order of Miscarriages, Premature Births, and Stillbirths.—One hundred and fifty-one families experienced one or more miscarriages, premature births, or stillbirths.[11] These unsuccessful pregnancies occurred before and after the birth of the malformed offspring, more often than they did preceding and following the births of the normally developed brothers and sisters. The development of the resulting offspring is unknown, nor is it understood to what extent malformations are associated with miscarriages, premature births, and stillbirths. Mall[4] has shown that many aborted embryos are malformed, and the present study indicates that at least 25 per cent of malformed individuals are stillborn. There is reason, therefore, to believe that at least some of the unsuccessful pregnancies may have given rise to malformed individuals. Regardless of the development of the offspring, miscarriages, premature births, and stillbirths would seem to represent expressions of reproductive inefficiency.

Relative Sterility Before Birth of Malformed Child.—The lengths of the intervals occurring between 2,146 pregnancies of the mothers of malformed children were determined.[12] A *long* period of relative sterility occurred *four times more often*, immediately preceding the conception of malformed offspring, than it did preceding the births of the normally developed brothers and sisters. This is interpreted as indicating that at this time the germ cells were too abnormal for fertilization to occur.

Frequency of Malformations Among Brothers and Sisters.—Two hundred and seventy-five mothers became pregnant *after* the births of their defective children.[13] The incidence of malformation among these subsequent offspring was approximately 18 to 25 times greater than in the population-at-large.

Duplication of Malformations Among Brothers and Sisters.—Forty families each possessed two or more congenitally malformed children.[14] The defect observed in the first malformed child reappeared in a subsequent, malformed brother or sister in 46 per cent of instances.

Duplication of Malformations Among Distant Relatives.—In 39 cases, a distant relative of the malformed child exhibited a congenital malformation.[14] The latter defect was identical with that observed in the malformed child in 41 per cent of instances.

Duplication of Rare Defects.—Maldevelopment occurs more frequently in the *left* dome of the diaphragm than in the right dome. One mother gave birth in successive pregnancies to two children both exhibiting an absence of the *right* dome.[14]

Duplication of Defects Through Two Wives.—One father had a child with a right-sided harelip and cleft palate by each of two wives.[14]

Malformations According to Sex.—The ratio of males to 100 females, among the malformed children, and their normally developed brothers and sisters, is given in Table IV. Hydrocephalus, pyloric stenosis and harelip seemed to favor the males, while anencephalus was found more frequently among females.

TABLE IV. SEX RATIO

Showing the proportion of males to females among offspring in families having malformed children. Note preponderance of defective *males* in individuals with *hydrocephalus, pyloric stenosis, hare lip* and *cleft palate;* and the large number of *females* exhibiting *anencephalus.*

DESCRIPTION	MALES	FEMALES	MALES TO 100 FEMALES
Normal siblings	851	694	122.6
Malformed offspring	501	434	115.4
Hydrocephalus without spina bifida	114	67	170.0
Pyloric stenosis	49	16	306.0
Hare lip, cleft palate	30	16	187.5
Anencephalus	27	74	36.5

DISCUSSION

The above observations offer no evidence that environment plays a rôle in etiology. This may be due to limitations of the study. For example, such defects as amputations, which are believed to be due to amniotic bands, did not appear in the series of abnormalities which formed the basis for this report.

On the other hand, the remaining characteristics bearing upon etiology, all point to heredity as the most likely cause of malformation. These fall into four groups: (a) color, (b) sex ratio, (c) reproductive *in*efficiency and (d) the character of the defects which were seen in brothers and sisters.

Abnormalities were observed in white persons twice as often as in negroes, which fact would support the theory of a germinal origin for congenital defects. This high frequency of malformations in whites is of interest in view of the fact that syphilis is much more common in negroes. It might be concluded, from these observations, that syphilis is not an etiologic factor.

Certain defects afflicted one sex more often than the other. If spontaneously occurring malformations arise, primarily, from environmental influences, it would seem that the sexes should be affected with equal frequency.

Reproductive inefficiency was indicated by: (a) the long period of relative sterility frequently observed immediately preceding the birth of the malformed child, (b) the nearness of miscarriages, premature births and stillbirths to the malformation pregnancy, (c) the high incidence of malformed offspring born to older mothers, and (d) the increased frequency of congenital defects among brothers and sisters. Since these evidences of reproductive weakness, in very many cases, operated over a period of years, it seems likely that their origins rested upon defects within the germ cells, rather than upon abnormality in the environment.

Perhaps the single most convincing piece of evidence in favor of heredity is the frequent duplication of defects in brothers and sisters. This was observed in the case of the more unusual, and more serious malformations, as well as in the more common types of less serious ones.

From this investigation it is *not* possible to conclude that *spontaneously occurring*, human, congenital malformations *do not* arise from factors inherent in the environment of the ovum. On the other hand, no evidence was found to confirm this theory. All of the available data point to heredity as the cause of maldevelopment.

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DISCUSSION

DR. WILLIAM A. SCOTT, TORONTO, ONT.—In attempting to evaluate "environmental" and "hereditary" factors, it is necessary to define rather precisely just what is meant by the terms. For instance, Muller subjected the fruit fly to the action of x-rays and produced gene mutations that had previously arisen spontaneously in fly colonies. The treated flies, however, showed 150 times more mutations than the untreated controls. These mutations, of course, were due to "environment," but, as they bred true to type, the changes in their offspring were the result of "hereditary" causes. What began from environment became hereditary. If we wish to try and separate such factors should we not think of them as falling into three possible groups? 1. Hereditary factors, affecting the chromosomes and being transmitted as either dominant or recessive characteristics. 2. Constitutional factors, affecting the germ plasm before fertilization. 3. Environmental factors, affecting the development of the ovum after fertilization. It would be understood, of course, that experimental work has shown that external influences may affect any one of these classes.

Dr. Murphy has shown that "disturbed pregnancies" occur more frequently than would be expected by chance in the pregnancies immediately preceding and immediately following the pregnancy which ended in the birth of the defective child, and Mall has pointed out that many aborted embryos are pathologic. Two explanations of this are possible. Faulty implantation of the ovum may result in deficient nourishment and injury to some of the cells of the early ovum, or an abnormal ovum may tend to have poor implantation and be liable to abort.

During the last two years we have had 16 cases of fetal deformities and one of hemorrhage of the newborn, the latter following elective cesarean section. Two of these were complicated by placenta previa (12.5 per cent) and one by threatened abortion. In these cases, therefore, there were over 18 per cent with complicated pregnancies. Yet, during the same period, the incidence of fetal deformities was only 0.9 per cent of the total births. Our incidence of placenta previa was about the same as Dr. Murphy's, namely 24 cases or 0.8 per cent of total deliveries. In the same series, there were 18 cases of macerated fetuses, 14 of whom had complicated pregnancies, in 9 the complication being toxemia of pregnancy.

Some hereditary deformities are manifested only when marriage occurs between suitable persons. I have a patient with two normal babies. She was one of a family of six, all of whom had either unilateral or bilateral congenital hip disease, yet in a careful inquiry no evidence of the disease could be discovered in the families of either her father or mother. It would appear that this tendency is a recessive characteristic of both her father and mother.

Without figures to substantiate my opinion, I have had the impression that certain types of fetal abnormalities, particularly mongolian idiocy, tend to arise in pregnancies occurring in the latter part of the childbearing period.

One occasionally sees cases where there appears to be a combination of hereditary and environmental factors. One of my patients gave birth to a baby with an amputation of the right leg just above the knee. This is usually accepted as an environmental occurrence, but the same child had an absence of the anterior chest and abdominal walls and an imperforate anus. She has since had a normal child.

It was very surprising to learn that the percentage of deformities in white people was double that of the colored race. With the close intermarriage of the latter, one would have thought the tendency to malformations would have been accentuated.

DR. WILLIAM R. NICHOLSON, PHILADELPHIA, PA.—I am interested in the type of malformation in which you cannot find any inheritance factor. Many years ago I delivered a patient whose family had a perfectly normal history so far as malformations were concerned. The mother had had one child by a former husband, who

was perfectly healthy. In this labor she delivered a child with agglutination of the toes and fingers, a microcephalic head with some hydrocephalus. Subsequently this patient had two perfectly normal children by the same husband. The interesting point in the history was that at the time this woman began her pregnancy she had a very queer undiagnosed condition of fever.

I contend therefore that developmental irregularities in these children may be due to acute disease of the mother.

I would include in the eight classes as given by Dr. Murphy, not only chronic disease but certain types of acute disease as well.

Looking over my statistics, upon the work of the midwives of Philadelphia since 1914, I found among the 96,000 cases which we have delivered 184 deformities among the children. Strangely enough, while Dr. Murphy states that he has had no amputations, in our list we had 7 amputations, none of which we thought were due to amniotic bands.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—During the 1918 influenza epidemic quite a number of monstrosities occurred in my own practice and in that of others. It was noticed that these women had had the "flu" in the early part of their pregnancies.

Dr. Williams, a veterinarian of Cornell University, reports that cattle on the range produce fewer monstrosities than cattle that are held under so-called civilized and wholly modernized conditions.

DR. EMIL NOVAK, BALTIMORE, MD.—Among the hereditary factors which Dr. Murphy enumerated is one which he spoke of as reproductive deficiency. In cases of endocrinopathic sterility I have been impressed with the relative frequency of congenital fetal deformities in those patients in whom pregnancy has occurred, perhaps after long-continued treatment. For example, a woman of about forty finally conceived after a primary endocrinopathic sterility of seventeen years, and at full term was delivered by cesarean section of a child which died shortly after birth of congenital cardiac abnormality. In another recent endocrinopathic case, pregnancy occurred after several years' treatment for sterility, but the baby was an anencephalic monster. And I might enumerate still other cases of this type. Such experiences are inclined to temper, at least slightly, one's enthusiasm in the treatment of endocrinopathic sterility.

THE CONTINUOUS AUSCULTATION OF THE FETAL HEART BY MEANS OF AN AMPLIFYING STETHOSCOPE*

Preliminary Report

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THE importance of the continuous auscultation of the fetal heart during labor, and particularly during delivery, is unquestionable. Early manifestations of fetal distress could be more often recognized if it were possible to auscultate the fetal heart continuously. The uncertainty and shortcomings of present-day methods are well known and keenly appreciated.

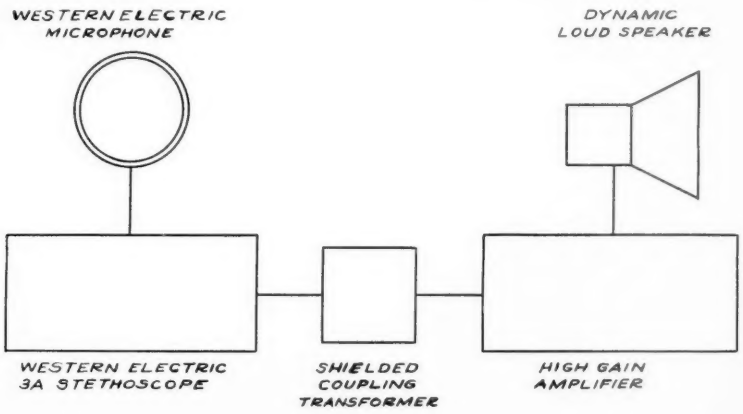

Fig. 1.

There have been many methods and systems devised for recording the fetal heart tones but up to the present none of these have proved satisfactory. They are, for the most part, too complicated and expensive for general use.

Because of the vast improvement in sound reproduction, all experiments prior to 1927 can be disregarded, although the experimental results with the various types of fetal cardiographs are pretty well borne out by modern methods of sound reproduction.

The first investigator to use modern methods of sound reproduction for recording the fetal heart tones was Dr. T. Cioslowski, of Warsaw (1932). His apparatus consisted essentially of: (1) microphone, (2) amplifier, (3) a more powerful amplifier, and (4) ear phones or megaphone. This apparatus was demonstrated

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before the Gynecological Society of Warsaw in 1932. The instrument did not meet with favor and has not, to my knowledge, been put on the market for general use.

Fig. 2.

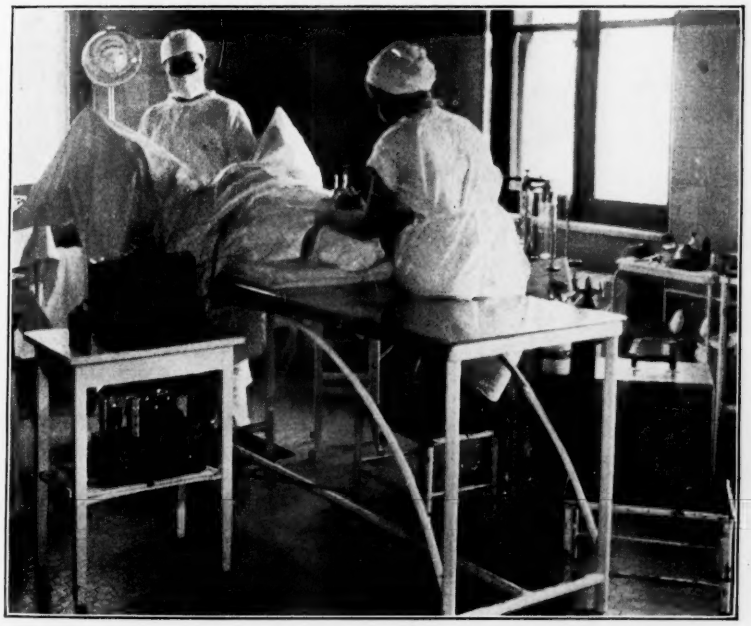

Fig. 3.

Another system, devised by Fillippo Nota, called "the electro-acoustic registration of the fetal heart tones by means of a constant density system" (1934), is a very

complicated affair and utterly unsuited for general use. It should, however, be stated in fairness to Professor Nota, that his method is very accurate and valuable in detecting pathologic defects in the fetal, as well as maternal, heart tones.

We have strived to devise a system for the continuous auscultation of the fetal heart by means of an amplifying stethoscope.* To carry out this idea we have employed a Western Electric No. 3A stethoscope with a dynamic microphone of contact type. The microphone is encased in sponge rubber with convenient attachments for fastening it to the patient's abdomen. The output of the Western Electric stethoscope is fed into a specially shielded coupling transformer and the output of this transformer is in turn fed into a high gain amplifier which drives a 10-inch dynamic loud speaker. The loud speaker is insulated from acoustic feed-back into the microphone which otherwise would cause a "howl" and destroy the desired fetal heart beats. With such a "hook-up" the fetal heart tones can be heard continuously for any length of time (Fig. 1). After placing the microphone over the fetal heart, i.e., over the area of the mother's abdomen where the fetal heart sound is loudest, the operation is simple; plug in; tune in; and listen (Figs. 2 and 3).

This system is far from perfect. It is expensive and somewhat cumbersome and therefore not generally practical, even for hospital use. However, we believe that the idea is right and already have plans for a much more compact and therefore easily portable system which will be far less expensive and much more efficient.

I wish to express my sincere appreciation to Dr. Albert Hersheimer, Resident Obstetrician, who has given many excellent suggestions and rendered very valuable assistance throughout this work.

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(1) *Nota, Fillippo:* Boll. d. Soc. piemon. di obst. e ginec. **2:** 388, 1934. (2) *Cioslowski, T.:* Ginek. polska **11:** 243, 1932. (3) *Beruti, Josué A.:* Rev. espan. de obst. y ginec. **10:** 53, 1925. (4) *Beruti, Josué A.:* Ref. in Bericht. über d. ges. Gynäk. u. Geburts. **8:** 323, 1925. (5) *Roscher:* Ztschr. f. Exper. Med. **39:** 131, 1924. (6) *Sachs:* Pflüger's Arch. f. d. ges. Physiol., 1923. (7) *Hofbauer, J., and Weiss, O.:* Zentralbl. f. Gynäk. **32:** 429, 1908.

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(The Transactions of the American Gynecological Society are included in the November issue, excepting the papers by Drs. J. R. Goodall, K. M. Wilson, and Prof. K. de Snoo.)

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Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Cesarean Section

Hoffström, K. A.: A Series of 100 Cesarean Sections, Acta obst. et gynec. Scandinav. **14**: 1, 1934.

From 1906 to 1933, 100 cesarean sections were performed among 20,892 women at the Lying-In Hospital in Tammerfors, giving a frequency of 0.5 per cent. This figure has, however, increased during the last three years, amounts now to 1.8 per cent. Classic operations were performed 36 times, cervicocorporeal 56 times and the purely cervical operation 8 times. No complications ensued in 73 per cent of the cases. The puerperal morbidity amounted to 27 per cent and comprised 24 cases with mild and 2 with grave puerperal disturbances. Five cases terminated fatally but none of them had any connection whatsoever with the operation. Hence the operation mortality is zero. The corrected mortality for the child was 1 per cent. The following three indications were the chief causes for the operation: (1) Disproportion between the infant's head and the pelvis, (2) profuse hemorrhage from placenta previa while the cervical canal was still undilated, and (3) eclampsismus and eclampsia in which a purely expectant treatment or a conservatively active treatment was unsuccessful or in which the eclampsia was of very grave character.

Seventeen patients became pregnant again after a comparatively short time. Six of these cases terminated spontaneously.

J. P. GREENHILL.

Smith, Judson A.: Cesarean Section at the Boston Lying-In Hospital, Surg. Gynec. Obst. **57**: 621, 1933.

From 1894 to 1931, inclusive, 1,556 cesarean sections were done at the Boston Lying-In Hospital, with a mortality of 4.9 per cent. Of these, 913 were primary sections. Of the primary sections 527 (58 per cent) were done for disproportion or cervical dystocia without other indications or complications. At the present time only about one-third of the primary sections are for this indication. Of the other primary sections 95 were performed chiefly for heart disease, 73 for toxemia or nephritis, 76 for premature separation of the placenta (including some toxic cases), 44 for placenta previa, and 98 for a variety of miscellaneous indications. The use of cesarean section for cardiac patients who have not had heart failure and have no other indication has diminished. The use of section delivery for placenta previa has increased. The incidence of primary sections for disproportion or cervical dystocia has decreased from a peak of 12 per thousand deliveries 15 years ago to a level of 5 per thousand deliveries during the past 4 years, indicating a much more conservative attitude. The total incidence of sections has been close to 30 per thousand deliveries for the last 16 years.

About one-half of the cesarean sections now are repeat sections. Although fewer cesareans are done now for suspected disproportion the incidence of primary section

remains at about 16 per thousand because of the extension of the indications for cesarean section. The mortality of primary section for uncomplicated disproportion or cervical dystocia is now about 1 per cent. The mortality of repeat operations is now about 3 per cent. That the mortality in general is now about 4.5 per cent is due mainly to the high death rate in primary section on patients with impaired cardiac or renal function. The infant mortality varies according to the group considered. For disproportion it has been about 2 per cent for the past 16 years, about half the deaths being due to congenital anomalies. In the group of repeat sections during the same period fetal mortality has been nearly 4 per cent, the increase being due mainly to the larger number of premature infants delivered by repeat operations. In the groups of toxemic, nephritic, and cardiac patients there is a high neonatal death rate due to prematurity, which raises some doubt as to whether cesarean is any better than pelvic delivery for these premature infants.

WM. C. HENSKE.

Hudnall Ware, H., Jr.: Cesarean Section in Richmond, Virginia, Virginia M. Month. 63: 82, 1936.

This is a statistical survey of the 127 cesarean sections done in Richmond during a five-year period. The figures show that the number of sections increased from 4.2 to 9.4 per thousand births between the first and last years of the study, the average incidence being 2 per cent of all hospital deliveries. The mortality was 8.8 per cent. The author draws the following conclusions from his figures: The duration of labor and rupture of membranes are important factors in increasing the maternal mortality following section. The maternal mortality rate was materially reduced by the use of the two-flap low cervical operation, particularly in potentially infected cases. The mortality rate was 8.60 per cent for primiparas and 1.81 per cent for multiparas.

EUGENE S. AUER.

Bue, Palliez, and Gernez: The Low Cesarean Section at the Charité Obstetrical Clinic During the Last Five Years, Bull. Soc. d'obst. et de gynéc. 26: 202, 1937.

The authors report a consecutive five-year series of 131 low cervical cesarean sections which were performed without any maternal death. These cases represented an incidence of 2.47 per cent in a series of 5294 labors. The fetal death rate among these 131 sections was 6.87 per cent. In 101 cases spinal anesthesia was used and it yielded excellent results in three-fourths of the instances. The authors believe their favorable results are attributable at least in part to the use of spinal anesthesia.

J. P. GREENHILL.

Voron, Brochier, and Boulez: Fourteen Cases of Hysterotomy for Placenta Previa in the Obstetrical Clinic of Lyon, Bull. Soc. d'obst. et de gynéc. 25: 475, 1936.

The authors report 14 cesarean sections performed for placenta previa since September, 1932. All were done under spinal anesthesia except two in patients who had a severe anemia with hypotension; the anemia was so severe that transfusions had to be given during operation. All of these cesarean sections were of the low, cervical type in spite of the fact that the placenta was in the lower uterine segment. There was not a single maternal death. Hence, the authors believe that this operation is the procedure of choice in serious cases of placenta previa.

J. P. GREENHILL.

Trillat, P.: The Treatment of Placenta Previa by Low Cesarean Section, Bull. Soc. d'obst. et Gynéc. **25:** 715, 1936.

Among 16,500 deliveries the author encountered 104 cases of placenta previa. The maternal death rate in this series was 10.5 per cent. Ten cesarean sections were performed without any deaths. The entire fetal mortality was 67.7 per cent but among the 10 cesarean sections there was only one fetal death, hence the fetal mortality for the cesarean section group was only 10 per cent. Because of these good results, the author has performed more cesarean sections for placenta previa during the last few years.

J. P. GREENHILL.

Brindeau, A.: The Different Types of Anesthesia for Cesarean Sections, Paris méd. **25:** 499, 1935.

The author reports a series of 100 cesarean sections performed under spinal anesthesia. This anesthesia proved entirely satisfactory in 84 cases but in 12 others general anesthesia was necessary. There were no deaths nor serious complications in this series. However, in the years preceding this group of sections, the author encountered three deaths during operation following spinal anesthesia. In spite of these sudden deaths, Brindeau believes that spinal anesthesia is the ideal one for cesarean section. He recommends local infiltration anesthesia for very sick women, for abdominal hysterotomies before full term and for the ligation of the fallopian tubes to produce sterility. He reserves general anesthesia for women who refuse spinal anesthesia, in whom lumbar puncture cannot be carried out and for those in whom spinal anesthesia does not produce satisfactory anesthesia.

J. P. GREENHILL.

Ginglinger, A.: The Type of Anesthesia Employed for Cesarean Section, Bull. Soc. d'obst. et de gynéc. **26:** 367, 1937.

Among 237 cesarean sections performed under ether anesthesia, there were 4 deaths which Ginglinger believes could be attributed to the anesthesia. Two of these deaths were due to bronchopneumonia and two to hemorrhage produced by atony. The latter two patients died on the operating table. Among 248 cesarean sections done under spinal anesthesia there were three deaths due to immediate syncope after the introduction of the anesthetic. The author urges that local anesthesia should be used for cesarean sections. Ether should be reserved for urgent cases such as placenta previa and prolapse of the cord. Spinal anesthesia should be used only in obese women where difficulties may be encountered during operations.

J. P. GREENHILL.

Banister, J. Bright: Present Position of Cesarean Section in Obstetric Practice, Brit. M. J. **2:** 1143, 1935.

The author believes that cesarean section occupies an unjustifiable position in obstetric practice today, that the incidence of the operation is far too high, that the indications for its use are at present too wide, and that it is attended by too high a maternal mortality rate. Such belief is supported by figures from several clinics, and by the widespread indications for the operation as cited by Amand Routh—in all, twenty-four indications under the main headings of (1) obstruction to labor, (2) uterine hemorrhage, and (3) constitutional crises.

In a series reviewed here the mortality rate was 6.6 per cent. The gross mortality rate following childbirth in England and Wales is 0.45 per cent. The mortality rate in 1,763 cases of cesarean section performed in England in famous maternities by experienced and distinguished operators was 5.8 per cent. The author states that the foremost reason for the widespread use of the operation is the purely surgical outlook upon obstetric problems. The baby is aimed at to be "let out" like pent-up pus by the surgically wise but obstetrically foolish.

The author believes that nature's powers and technique are safer and nature's way of overcoming moderate degrees of disproportion infinitely greater than we imagine to be the case and that a trial labor cannot truly be called such, until true second-stage pains have been present for some time.

F. L. ADAIR AND S. A. PEARL.

Crichton, E. C.: Indications for Cesarean Section, South African M. J. 8: 595, 1934.

The author devotes the bulk of the article to the relative indications.

Because of the relatively high maternal mortality in the series of sections investigated by the author (11.5 per cent) he feels that cesarean section has a minor place in the treatment of placenta previa which gives only a 4.75 per cent maternal mortality when treated by the Braxton Hicks method.

In eclampsia sections should only be employed in cases of disproportion and in rare cases which have improved under conservative treatment but appear to be in imminent danger of recurrence of severe symptoms.

In heart disease the author prefers delivery by the natural route supporting the patient with morphia in the first stage and expediting the second stage with forceps under chloroform anesthesia.

The author believes that patients who previously had a section for any reason other than disproportion may be subjected to a test of labor.

Where disproportion exists the author believes in a test of labor. If the head is descending and the cervix is dilating, the author waits until the cervix has been dilated for an hour before deciding upon the method of delivery.

If the head remains high he resorts to a lower segment cesarean section.

F. L. ADAIR AND I. C. UDESKY.

Jensen, Julius: The Management of Heart Disease in Pregnancy, South. M. J. 29: 572, 1936.

The management of heart disease in pregnancy is guided by the state of compensation. Most women with heart disease bear children without added discomfort. With close prenatal supervision patients with early decompensation will be detected. This is important because congestive failure advances rapidly in pregnant women.

When cardiac failure develops, it should be treated first by bed rest, and digitalis and morphine used as indicated. With too prolonged bed rest cardiovascular tone is impaired. The patient who does not improve upon this regime to the extent where she can withstand moderate physical effort should not go to spontaneous labor.

Early interruptions of pregnancy for cardiac reasons are rarely indicated. Premature induction of labor insures a favorable proportion between the maternal pelvis and the child and is, therefore, often advisable. Where sterilization is indicated, delivery may be effected by cesarean section.

ARNOLD GOLDBERGER.

Andrews, C. J., and Nichills, Richard B.: Unusual Indications for Cesarean Section, Virginia M. Month. **63**: 33, 1936.

The authors present a series of 1,200 consecutive deliveries with a cesarean section incidence of 2.7 per cent, or 34 cases, with no maternal mortality. They have listed as unusual indications for section all cases outside of those with a contracted pelvis. The unusual indications were: Dystocia following intrauterine radium applications, double uterus, pregnancy in the rudimentary horn of the uterus, torsion of tube complicating labor, pregnancy following the successful repair of vesicocervical fistula, eclampsia, abruptio placentae, and fibroids complicating labor. There were fourteen of these unusual indications.

EUGENE S. AUER.

De Guchteneere, Lahaye, and Foulon: Cesarean Section as a Method of Therapy to Maintain the Circulation of the Cord, Bruxelles-méd. **15**: 611, 1935.

The clinical picture of hypertonicity of the parturient uterus, in the absence of any obstacle in the pelvis, and with signs of fetal distress ought to make one think of obstructor circulation of cord vessels. This condition can be relieved only by cesarean section. It occurs more often in the young girl than in the multipara.

J. THORNWELL WITHERSPOON.

Bud, G.: Cesarean Section in the Long Axis, Monatschr. f. Geburtsh. u. Gynäk. **98**: 210, 1934.

When a cervical cesarean section is performed, the incision in the lower uterine segment is generally made vertically. However, since in most cases the uterus is rotated to the right, this vertical incision, after the child has been removed from the uterus, runs obliquely toward the left tubal corner. Hence the author makes the incision of the lower uterine segment obliquely directed to the right tubal corner. After the child has been removed this incision then runs vertically.

J. P. GREENHILL.

Fleischer, A. J., and Kushner, J. I.: Experiences With the Latzko Cesarean Section, Surg. Gynec. Obst. **62**: 238, 1936.

The Latzko operation is a valuable adjuvant in the armamentarium of every obstetrician. It should not be used promiscuously, but rather is indicated in all cases which cannot be delivered by the vaginal route when there is a temperature indicative of a potential infection and also in patients with normal temperatures, who have been repeatedly examined vaginally or when membranes have been ruptured for a long time.

The operation does entail some technical difficulties which can be overcome by any obstetrician with a sound surgical background and training. It is not a panacea for all frankly infected cases. DeLee's dictum is very appropriate: "Laparotrachelotomy for all but those where infection is suspected, then Latzko's operation, Porro, or craniotomy."

WM. C. HENSKE.

Riddell, James: Lower Segment Caesarean Section, Brit. M. J. **1**: 792, 1936.

The author points to the advantages of the low cervical cesarean section in contrast to that of the classical operation. A trial of labor is possible; the operation can be performed prior to or after the onset of labor; no haste is required during the operation; the contractile part of the corpus is not invaded; bleeding is less and,

therefore, there is less danger of shock and sepsis. Convalescence is smoother. The suture line is low down and less likely to cause adhesions between omentum, bowel or uterus and abdominal wall. The operative technique is outlined, and the recommendation for preoperative x-ray study is made.

F. L. ADAIR AND S. A. PEARL.

Basden, Margaret M.: Caesarean Section in Infected Cases, Brit. M. J. 1: 358, 1936.

A series of 45 cases over 11 years is reported. Some were frankly infected, others potentially so. No mortality occurred in this series.

The author believes the pendulum has swung too much in the direction of conservatism, and that though there are definite risks present, there is still a possibility of saving a certain number of infants and mothers by performing the operation in potentially infected cases. The possible dangers of a difficult instrumental delivery are not always realized. Case records are given. The low cervical operation was done in 16 cases only. The author performs this operation more commonly at the present time. Two cases had cesarean hysterectomies. This is advocated when the risk of infection appears very great.

F. L. ADAIR AND S. A. PEARL.

Gustafson, Gerald W.: An Eight-Year Survey of Cesarean Sections at the William H. Coleman Hospital, Surg. Gynec. Obst. 64: 1035, 1937.

The greatest single factor in the reduction of cesarean section mortality at the Coleman Hospital has been the wider adoption of low cervical cesarean section.

The low cervical operation is safer than the classic, not only in cases of patients having had tests of labor but also in elective cases. In the latter type of patients and in other patients having short lower uterine segments, the transverse incision with the Phaneuf technique is a very satisfactory procedure.

It is reasonable to assume that if low cervical operations could be substituted for the classic operations in this country, the mortality from abdominal deliveries would be cut in half.

WM. C. HENSKE.

Pemberton, John: Six Cesarean Sections on the Same Patient, Lancet 2: 1039, 1936.

The report of six cesarean sections on a single patient is unusual. In the last sixteen years one physician has done all six sections on this patient for a generally contracted pelvis. Each operation was elected about ten days before the estimated term date. There was only one abdominal scar and no omental or bowel adhesions, although the uterus was adherent to the abdominal wall. All puerperal periods were afebrile. The uterine wall was not unusually thin at the site of the scar.

References are made to one case having seven cesarean sections, another six.

H. CLOSE HESSELTINE.

Thiessen, P.: The Avoidance of Complications in Cesarean Sections Performed Under Spinal Anesthesia, Med. Klin. 32: 416, 1936.

The author describes his technique for spinal anesthesia in performing cesarean sections. He believes that this form of anesthesia is excellent for cesarean sections and is without any danger. However, one must be careful to observe all precautions.

J. P. GREENHILL.

Voron, Brochier, and Magnin: Parotitis After Low Cesarean Section, Bull. Soc. d'obst. et de gynéc. **25:** 251, 1936.

The authors report 3 cases of parotitis which occurred soon after cervical cesarean sections. All 3 women had defective teeth, hence the authors believed they present evidence of a buccal origin of parotitis. Since spinal anesthesia was used in 2 cases, there could not have been any injury in the maxillary region. In spite of the large number of cases of parotitis which have occurred after gynecologic operations, only one case could be found following cesarean section in a series of 520 cases of parotitis collected from the literature. In fact, parotitis is rare after labor because in a series of 25,000 labors reported from the Koenigsberg clinic there were only 9 cases of parotitis. The authors' case was the only one they observed after 100 cesarean sections.

J. P. GREENHILL.

Huessy, P.: Our Deaths From Cesarean Section, Monatschr. f. Geburtsh. u. Gynäk. **103:** 16, 1936.

In the author's clinic from 1921 to 1935 a total of 810 cesarean sections were performed. In this series there were 28 maternal deaths, an incidence of 3.45 per cent. Mortality in the clean cases was 0.37 per cent, in the unclean cases 1.23 per cent. The actual operative mortality was 1.6 per cent. The author warns that it is best to perform cesarean sections only upon clean cases except where it is absolutely necessary to operate on unclean cases. In clean cases there should be no fetal mortality of viable babies and the maternal death rate should not exceed 1 per cent at the very most. When the results of the mother and child are considered together, cesarean section is superior to vaginal operative deliveries. Cesarean section is not a serious operation when it is properly performed for a proper indication and under the proper conditions. The author recalls that even after spontaneous delivery there is a distinct maternal mortality, especially from embolism which does not occur less frequently than after cesarean section. The author believes that in the interest of the child the indications for cesarean section should be extended.

J. P. GREENHILL.

Lindsay, Douglas: Pathological Results of Cesarean Section, Lancet **1:** 19, 1934.

To stress the importance of operative complication of cesarean section, the author reports the removal of two urinary bladder calculi, one of which was attached to a silk suture from the old uterine scar. Since the only symptom was menorrhagia, the bladder stones were discovered only by routine pelvic examination. No explanation is offered for the silk suture extending into the bladder. The stones were the size of grapes and were phosphatic.

The author states that menorrhagia, abdominal adhesions or uterine fistulas are the more frequent conditions demanding hysterectomy following cesarean sections. Moreover, it is stated that cesarean section operations are abused as much as are forceps and are undertaken often by unqualified operators. Certain errors predominate in the closure: (a) poor reconstruction of uterine wall, (b) infection from poor technique and improper management of patient, and (c) incorrect use of suture and suture material.

Although silk sutures are important for the first row, it is stressed that they must be buried, interrupted and not heavier than a number 3 catgut. Catgut sutures are used also to approximate the muscle and to fix the visceral peritoneum. In the author's series of nearly 200 operations none required later hysterectomy for complication of the sections.

H. CLOSE HESSELTINE.

Orrul, Michale: Placental Insertion in the Mechanism of the Rupture of the Uterus Corresponding to Cesarean Section Scar, Clin. ostet. **15:** 569, 1936.

The author describes a case of twin pregnancy with spontaneous rupture of the uterus in the seventh month. He found placental insertion to have gone deeper into the scar than ordinarily found.

In a second case he reports that the placenta was completely developed into the scar tissue. The rupture of the uterus in this case was complete.

The author emphasizes the predisposing factor created by placental insertion on scar tissue of the uterus. He concludes that the excessive distention of the uterus due to multiple pregnancy is a further predisposing factor for rupture of a section scar. He believes, as many authors at present do, that a low cervical cesarean section would render placental insertion on scar tissue less likely than a classical section.

AUGUST F. DARO.

Trillat, Paul: The Distant Consequences of the Low Cesarean Section, La Gynécologie **33:** 743, 1934.

The cervical cesarean section has very few late disturbances and permits the normal development of subsequent pregnancies. Spontaneous labor is possible if the pelvis is sufficiently roomy. However, one should not use any medical oxytocics and should avoid all obstetric maneuvers which require force. Since every woman who has had a cesarean section may develop a rupture of the uterus, all labors after a cesarean section should be conducted in a hospital. However, ruptures of the uterus during pregnancy are rare after the cervical cesarean section. Trillat collected from the literature 39 cases of uterine rupture which have occurred following cervical cesarean section.

J. P. GREENHILL.

Fournier, F., and Estienny, E.: Rupture of a Scar During Labor Following a Cervical Cesarean Section, Bull. Soc. d'obst. et de gynéc. **25:** 185, 1936.

In 1934 Bonnet was able to collect from the literature 37 cases of rupture of the scar following the low, cervical cesarean section. Fournier and Estienny report an additional case in a woman who had twins. The authors believe the rupture was not due to weakness of the scar but to excessive distention and unusual thinning resulting from the presence of a twin pregnancy. The rupture did not occur until after a number of hours of severe uterine contractions. The authors maintain that a scar in the upper part of the uterus would likewise have ruptured under these conditions.

J. P. GREENHILL.

Andérodias and Péry: Spontaneous Labor in Women Who Previously Had Low Cesarean Sections, Bull. Soc. d'obst. et de gynéc. **24:** 552, 1935.

The authors report a series of 16 women who had vaginal deliveries after having previously been delivered by low, cervical cesarean sections. The indications for the cesarean sections had been contracted pelvis in 11, anomalies of cervical dilatation in 4, and retroplacental hemorrhage in 1. In 9 of the 16 cases forceps were prophylactically applied when the head was at the outlet but in seven instances delivery was entirely spontaneous.

J. P. GREENHILL.

Items

American Board of Obstetrics and Gynecology

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 6, 1937 and Saturday, February 5, 1938. Application for admission to these examinations must be filed on an official application form in the office of the Secretary at least sixty days prior to these dates.

The general oral, clinical, and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1938.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Mississippi Valley Medical Society

The Mississippi Valley Medical Society offers a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on a subject of interest and practical value to the general practitioner of medicine. Entrants must be ethical licensed physicians, residents of the United States and graduates of approved medical schools. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society (September 28, 29, and 30, 1938), the Society reserving the exclusive right to first publish the essay in its official publication—the Radiologic Review and Mississippi Valley Medical Journal. All contributions shall not exceed 5,000 words, be typewritten in English in manuscript form, submitted in five copies, and must be received not later than May 15, 1938. Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

Erratum

In the article by John I. Brewer and James E. Fitzgerald entitled "Six Normal and Complete Presomite Human Ova," published in the August issue of the JOURNAL, Fig. 16 was unfortunately omitted. It is published below together with several paragraphs in which its mention occurred.

FITZGERALD OVUM

The specimen was obtained by abdominal hysterectomy. The operation was performed because of multiple large fibromyomas. The patient had a normal thirty-day menstrual cycle, and there was no accurate coital history. The hysterectomy was performed on the thirty-fifth day of the cycle.

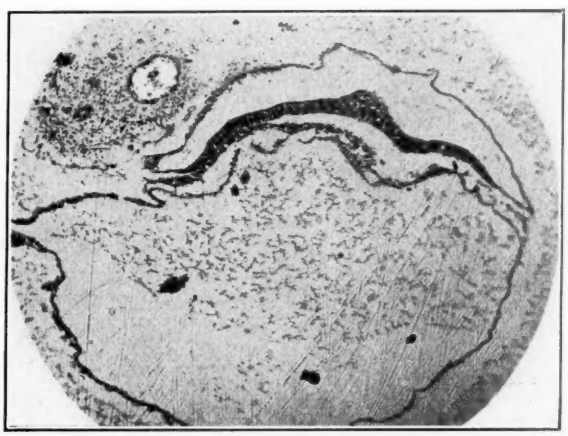

Fig. 16.—The Fitzgerald ovum. This photomicrograph is made of a sagittal section of the embryonic disc. Hensen's node is distinctly elevated. The primitive streak is well defined. The yolk sac is larger than the amnion. In the substance of the body stalk, there is an amniotic duct.

The uterus was as large as a large grapefruit. It contained many subserous and intramural fibroids. The endometrium was without gross pathologic changes. The blastocyst was embedded on the posterior wall of the endometrium in the fundal area and was definitely elevated above the decidual level. The measurements of the ovum are: External chorion 14 by 12 by 9 mm., internal chorion 11 by 10.5 by 5 mm., embryonic disc 1.085 by 0.6 mm., amnion 1.1 by 0.7 mm., and yolk sac 1.3 by 1.2 by 1.4 mm.

There was a primitive streak including Hensen's node (Fig. 16). The blastocyst was covered with branched villi which were as long as 1 mm. The ovum was sectioned in a plane which deviates but slightly from the longitudinal. All sections were saved and arranged serially. A complete reconstruction of the embryo was made through the courtesy of Dr. George Streeter, and drawings of the model were made by James F. Didusch.